

Manual of

**CARDIOVASCULAR
MEDICINE**

FOURTH EDITION

Section Editors

Leslie Cho, MD, FACC

Section Head
Preventive Cardiology & Rehabilitation
Director, Womens Cardiovascular Center
Cleveland Clinic
Cleveland, Ohio

Esther S.H. Kim, MD, MPH

Staff Physician
Sections of Vascular Medicine and Preventive Cardiology
Cleveland Clinic
Cleveland, Ohio

Richard A. Krasuski, MD

Director
Adult Congenital Heart Disease Services
Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio

W.H. Wilson Tang, MD, FACC, FAHA

Staff Cardiologist
Department of Cardiovascular Medicine,
Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

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EDITOR

Brian P. Griffin, MD, FACC

The John and Rosemary Brown Endowed Chair in Cardiovascular Medicine
Director, Cardiovascular Medicine Fellowship Program
Cleveland Clinic
Cleveland, Ohio

Associate Editors

Thomas D. Callahan, IV, MD, FACC, FHRS

Associate Director, Cardiology Fellowship
Cleveland Clinic
Cleveland, Ohio

Venu Menon, MD

Director, Coronary Care Unit
Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio

Guest Editors

Willis M. Wu, MD

Chief Fellow
Department of Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio

Clay A. Cauthen, MD

Fellow
Cardiovascular Medicine
Heart and Vascular Institute
Cleveland Clinic
Cleveland, Ohio

Justin M. Dunn, MD, MPH

Chief Fellow
Cardiovascular Medicine
Cleveland Clinic
Cleveland, Ohio



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Two Commerce Square
2001 Market Street
Philadelphia, PA 19103 USA
LWW.com

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First Edition © 2000 by Lippincott Williams & Wilkins

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Printed in People's Republic of China

Library of Congress Cataloging-in-Publication Data

Manual of cardiovascular medicine/editor, Brian P. Griffin; associate editors, Thomas D. Callahan, Venu Menon; guest editors, Willis M. Wu, Clay A. Cauthen, Justin M. Dunn. -- 4th ed.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-1-4511-3160-4 -- ISBN 1-4511-3160-7

I. Griffin, Brian P., 1956-

[DNLM: 1. Heart Diseases--diagnosis. 2. Cardiac Surgical Procedures--methods. 3. Heart Diseases--therapy.

WG 141]

616.1'2--dc23

2012007462

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*To our families and to the fellows and staff of
the Department of Cardiovascular Medicine,
Cleveland Clinic
—BG, VM, TC, WW, CC, JD*

CONTRIBUTORS

Unless otherwise noted, the following contributors are affiliated with the Cleveland Clinic Foundation, Cleveland, Ohio.

JoEllyn M. Abraham, MD

Cardiology Fellow
Cardiovascular Medicine

Kia Afshar, MD

Fellow
Department of Cardiovascular Medicine

Shikhar Agarwal, MD, MPH, CPH

Fellow
Cardiovascular Medicine

Imran N. Ahmad, MD

Interventional Cardiology Fellow
Department of Interventional Cardiology
Heart and Vascular Institute

Salim H. Ahmed, MD

Fellow
Cardiovascular Medicine

Olcay Aksoy, MD

Interventional Cardiology Fellow
Department of Cardiovascular Medicine

Saif Anwaruddin, MD

Fellow in Interventional Cardiology

Bryan J. Baranowski, MD

Staff
Department of Cardiovascular Medicine
Section of Cardiac Pacing and
Electrophysiology

Mosi K. Bennett, MD, PhD

Fellow
Cardiovascular Medicine

Michael P. Brunner, MD

Fellow in Cardiovascular Medicine
Cardiovascular Medicine

Matthew C. Bunte, MD

Fellow in Cardiovascular Medicine
Robert and Suzanne Tomsich Department
of Cardiovascular Medicine

**Thomas D. Callahan, IV,
MD, FACC, FHRS**

Associate Director, Cardiology Fellowship

Clay A. Cauthen, MD

Fellow
Cardiovascular Medicine
Heart and Vascular Institute

João L. Cavalcante, MD

Chief, Advanced Cardiovascular Imaging
Fellow
Cardiovascular Medicine

Matthew A. Cavender, MD

Fellow
Heart and Vascular Institute

Leslie Cho, MD, FACC

Section Head, Preventive Cardiology &
Rehabilitation
Director, Womens Cardiovascular Center
Department of Cardiovascular Medicine
Heart and Vascular Institute

Edmond M. Cronin, MB, MRCP

Electrophysiology Fellow
Section of Electrophysiology and Pacing
Department of Cardiovascular Medicine

Arun Dahiya, MD

Cardiac Imaging
Department of Cardiac Imaging

**Milind Desai, MD, FACC,
FAHA, FESC**

Associate Professor of Medicine,
Department of Cardiovascular Medicine
Heart and Vascular Institute

Sandeep Duggal, DO

Physician, Cardiovascular Disease

Justin M. Dunn, MD, MPH

Chief Fellow
Cardiovascular Medicine

Hemal Gada, MD, MBA

Cardiovascular Medicine Fellow
Cardiovascular Medicine

Sachin S. Goel, MD

Clinical Associate
Cardiovascular Medicine

Adam S. Goldberg, MD

Cardiovascular Medicine Fellow
Heart and Vascular Institute

Gonzalo Gonzalez-Stawinski, MD

Staff Cardiac Surgeon

Eiran Z. Gorodeski, MD, MPH

Assistant Professor of Medicine
Department of Cardiovascular Medicine
Lerner College of Medicine
Associate Staff
Department of Cardiovascular Medicine

Adam W. Grasso, MD, PhD, FACC

Staff Cardiologist,
Director of Cardiology Consult Service
Cardiovascular Medicine

Brian P. Griffin, MD, FACC

The John and Rosemary Brown Endowed
Chair in Cardiovascular Medicine
Director, Cardiovascular Medicine
Fellowship Program

Mary T. Quinn Griffin, PhD, RN

Associate Professor
Frances Payne Bolton School of Nursing
Case Western Reserve University
Cleveland, Ohio

Chetan Vagesh Hampole, MD

Fellow
Department of Cardiovascular Medicine

Mazen Hanna, MD

Staff Cardiologist

Anthony Hart, MD

Fellow
Cardiovascular Medicine

James E. Harvey, MD, MSc

Chief Interventional Cardiology Fellow
Heart and Vascular Institute

Christopher M. Huff, MD

Cardiovascular Medicine Fellow
Heart and Vascular Institute

Christopher Ingelmo, MD

Chief Cardiac Electrophysiology Fellow
Heart and Vascular Institute

Michael A. Jolly, MD

Interventional Cardiology Fellow
Department of Cardiovascular Medicine

Samir R. Kapadia, MD

Director, Sones Cardiac Catheterization
Laboratories
Director, Interventional Cardiology
Fellowship
Department of Cardiovascular Medicine

Esther S.H. Kim, MD, MPH

Staff Physician
Sections of Vascular Medicine and
Preventive Cardiology
Department of Cardiovascular Medicine
Cleveland Clinic Heart and Vascular
Institute

Richard A. Krasuski, MD

Director of Adult Congenital Heart Disease
Services
Cardiovascular Medicine

Amar Krishnaswamy, MD

Staff Physician
Division of Interventional Cardiology

Praneet Kumar, MD

Fellow
Cardiovascular Medicine

James E. Lai, MD

Fellow
Department of Cardiovascular Medicine

Evan Lau, MD

Interventional Cardiology Fellow
Cardiology

**Lee Fong Ling, MBBS, MMed,
MRCP, FAMS**

Consultant Cardiologist
Department of Cardiology
KTPH, Alexandra Health
Republic of Singapore

Jun-Yang Lou, MD, PhD

Fellow
Department of Cardiovascular Medicine

Christopher H. May, MD

Fellow in Cardiovascular Medicine
Department of Cardiovascular Medicine

Venu Menon, MD

Director Coronary Care Unit
Cardiovascular Medicine

Maria M. Mountis, DO

Cardiologist

Santosh S. Oommen, MD

Cardiac Electrophysiology Fellow
Department of Cardiovascular Medicine

Parag R. Patel, MD

Fellow
Department of Cardiovascular Medicine

Femi Philip, MD

Cardiology Fellow
Cardiovascular Medicine

Andrew N. Rassi, MD

Interventional Cardiology Fellow
Division of Cardiology
Massachusetts General Hospital
Boston, Massachusetts

Russell E. Raymond, DO

Cardiologist
Department of Cardiovascular Medicine

John Rickard, MD

Cardiac Electrophysiology Fellow

Marwa A. Sabe, MD

Fellow
Cardiovascular Medicine

Michael A. Samara, MD

Fellow
Department of Cardiovascular Medicine
Section of Advanced Heart Failure and
Transplant Cardiology

Jay D. Sengupta, MD

Fellow
Cardiovascular Medicine

Firas Al Solaiman, MD

Fellow
Heart and Vascular Institute

Tyler L. Taigen, MD

Cardiology Fellow
Department of Cardiovascular
Medicine

W. H. Wilson Tang, MD, FACC, FAHA

Staff Cardiologist
Department of Cardiovascular
Medicine,
Heart and Vascular Institute

Maran Thamilarasam, MD

Staff Cardiologist
Cardiovascular Medicine

Gus Theodos, MD

Interventional Cardiology Fellow
Interventional Cardiology

Donald Underwood, MD

Head, Electrocardiography Laboratory
Robert and Suzanne Tomsich Department
of Cardiovascular Medicine
Sydell and Arnold Miller Family Heart &
Vascular Institute

Amanda R. Vest, MBBS

Fellow in Cardiovascular Medicine
Heart and Vascular Institute

Willis M. Wu, MD

Chief Fellow
Department of Cardiovascular
Medicine

Omeed Zardkoobi, MD

Fellow in Cardiac Electrophysiology
and Pacing
Department of Cardiovascular
Medicine

**Peter Zimbwa, MBChB, MSc, DPhil,
MRCP, DTM&H**

Fellow
Cardiovascular Medicine

Edwin T. Zishiri, MD

Fellow
Cardiac Electrophysiology

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P R E F A C E

The 4th edition of the *Manual of Cardiovascular Medicine* has been extensively updated and revised. New chapters on diabetes and the heart, pulmonary hypertension, cardiovascular manifestations of systemic disease, percutaneous management of structural heart disease, and troubleshooting ventricular assist devices have been added. Examples of key electrocardiographic tracings have been added as has a quick reference list of often needed formulae. Our aim has been to make this an easy-to-use, up-to-date, portable reference for all those involved in the management of cardiovascular disease. We have included current guidelines from the American Heart Association/American College of Cardiology and other national and international cardiovascular societies where appropriate. We appreciate the feedback we have received concerning prior editions and suggestions as to how to improve the book.

This manual has been written by the current and past fellows and staff of the Department of Cardiovascular Medicine, Cleveland Clinic. I wish to thank all those who contributed to this and previous editions, especially Eric Topol, coeditor in prior editions and now at Scripps, San Diego, and Steve Marso now at Mid America Heart Center, Kansas City, coeditor of the 1st edition. I wish to recognize the associate editors of this edition, Venu Menon and Tom Callahan, who are associate directors of the Cardiovascular Disease Training Program at Cleveland Clinic and who have done a superb job in helping edit the manual and keeping it topical. The guest editors, Willis M. Wu, Clay A. Cauthen, and Justin M. Dunn, are or have been Chief Fellows in the Cardiovascular Training Program at Cleveland Clinic and have done a fine job of ensuring that the contributions were on time and comprehensive. The section editors, Leslie Cho, Esther S.H. Kim, Richard A. Krasuski, and W.H. Wilson Tang, have done a great job in ensuring the quality and topicality of their sections.

I wish to thank Lois Adamski, the educational coordinator of the Cardiovascular Disease Training Program at Cleveland Clinic, for having anchored the program over many years. Fran DeStefano, Leanne Vandetty, and everyone at Wolters Kluwer have been wonderful to work with. I remain deeply indebted to John and Rosemary Brown for endowing a Chair in Cardiovascular Medicine that supports my academic activity and for their wonderful friendship. I have learned much over the years from my colleagues and fellows at the Department of Cardiovascular Medicine at Cleveland Clinic and from my surgical colleagues in the Heart and Vascular Institute, Cleveland Clinic, and I thank all of them for their collegiality and kindness. Finally, I wish to express my immense gratitude to my family: to my parents for instilling in me a thirst for knowledge and to my wife Mary without whose support, patience, and fortitude this and all other endeavors would have been impossible.

Brian P. Griffin, MD

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SECTION

I

Ischemic Heart Disease

EDITOR

Venu Menon

Acute Myocardial Infarction

I. EPIDEMIOLOGY. Acute myocardial infarction (MI) is the leading cause of death in North America and Europe. Each year, an estimated 785,000 Americans will sustain a new MI, and another 470,00 will have a recurrent MI. An American has an acute MI every 25 seconds, and someone dies of an MI every minute. In 2007, coronary heart disease caused one out of every six deaths. The incidence and mortality with acute MI have declined dramatically over the last 30 years, with the advent of the coronary care unit, fibrinolytic therapy, catheter-based reperfusion, and statin therapy. The aging of the population in advanced economies, as well as the global increased incidence of diabetes and obesity, will however, increase the sequelae of atherosclerotic coronary artery disease in the future (1).

II. PATHOPHYSIOLOGY. In most patients, coronary plaque rupture is the initiating event of acute MI. Rupture of the fibrous cap of a coronary atheroma exposes the underlying subendothelial matrix to formed elements of circulating blood, leading to activation of platelets, thrombin generation, and thrombus formation. Erosion of a coronary plaque without rupture can also lead to thrombus formation and is estimated to cause up to 25% of MIs. Acute coronary syndrome (ACS) is a dynamic process that involves cyclical transitioning among complete vessel occlusion, partial vessel occlusion, and reperfusion. Occlusive thrombus in the absence of significant collateral vessels most often results in acute ST-segment elevation myocardial infarction (STEMI). The pathophysiology of STEMI and non-ST-segment elevation myocardial infarction (NSTEMI) is similar, and this explains the substantial overlap in ACSs with regard to ultimate outcome, extent of necrosis, and mortality rates. The recognition of ST-segment elevation is particularly important because it generally mandates the need for emergent reperfusion therapy.

III. DEFINITION. A 2007 expert consensus document (2) redefined acute MI as the detection of a rise and/or fall in cardiac troponin with at least one value above the 99th percentile of the upper reference limit (URL) utilizing an assay with < 10% coefficient of variation at the level of detection, together with evidence of ischemia. Ischemia was defined as any symptom of ischemia, electrocardiographic changes suggestive of new ischemia, development of pathologic Q waves on electrocardiogram (ECG), or imaging evidence of infarction. Included in the definition were sudden cardiac death (SCD) with evidence of myocardial ischemia (new ST elevation, left bundle branch block [LBBB], or coronary thrombus) and biomarker elevation > 3× URL for post-percutaneous coronary intervention (PCI) patients or > 5× URL for post-coronary artery bypass grafting (post-CABG) patients. Documented stent thrombosis was recognized in this new definition as well (Table 1.1). Established MI was defined as any one criterion that satisfies the following: development of new pathologic Q waves on serial ECGs, imaging evidence of MI, or pathologic findings of healed or healing MI.

TABLE 1.1 Clinical Classification of Different Types of Myocardial Infarction

Type 1	Spontaneous MI related to ischemia from a coronary plaque rupture or dissection
Type 2	MI due to ischemia resulting from increased oxygen demand or decreased supply
Type 3	Sudden cardiac death with symptoms of ischemia, new ST elevation, or LBBB or coronary thrombus
Type 4a	MI associated with PCI
Type 4b	MI associated with stent thrombosis
Type 5	MI associated with CABG

CABG, coronary artery bypass grafting; LBBB, left bundle branch block; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Adapted from Thygesen K, Alpert JS, White HD. Universal definition of myocardial infarction. *J Am Coll Cardiol*. 2007;50:2173–2175.

IV. CLINICAL DIAGNOSIS. In any patient with a clinical history of chest pain suspected to be of cardiac origin, an ECG should be obtained within 10 minutes of presentation and interpreted promptly to determine eligibility for reperfusion therapy. If the **ECG demonstrates acute ST-segment elevation or new LBBB, emergent reperfusion treatment with primary PCI or fibrinolysis is indicated.** During this evaluation period, a targeted medical history and physical examination should be performed. If the patient's history is compatible with cardiac ischemia and the ECG does not meet the criteria for reperfusion therapy, the patient may have unstable angina or NSTEMI. These syndromes are discussed in Chapter 2.

A. Signs and symptoms

1. The classic symptoms are severe, **crushing substernal chest pain** described as a squeezing or constricting sensation with frequent radiation to the left arm, often associated with an impending sense of doom. The discomfort is similar to that of angina pectoris, but it is typically more severe, of longer duration (usually > 20 minutes), and is not relieved with rest or nitroglycerin. Peak intensity is usually not instantaneous, as it would be with pulmonary embolism or aortic dissection.
 - a. The chest discomfort may radiate to the neck, jaw, back, shoulder, right arm, and epigastrium. Pain in any of these locations without chest pain is possible. Myocardial ischemic pain localized to the epigastrium is often misdiagnosed as indigestion. Acute MI can occur without chest pain, especially among postoperative patients, the elderly, and those with diabetes mellitus.
 - b. If the pain is sudden, radiates to the back, and is described as tearing or knife-like, aortic dissection should be considered.
2. Associated symptoms may include diaphoresis, dyspnea, fatigue, light-headedness, palpitations, acute confusion, indigestion, nausea, or vomiting. Gastrointestinal symptoms are especially common with inferior infarction.

B. Physical examination. In general, the physical examination does not add much to the diagnosis of acute MI. However, the examination is extremely important in excluding other diagnoses that may mimic acute MI, in risk stratification, in the diagnosis of impending heart failure, and in serving as a baseline examination to monitor for mechanical complications of acute MI that may develop.

1. **Risk stratification**, which aids in treatment decisions and counseling patients and families, is based in part on age, heart rate, and blood pressure and on the presence or absence of pulmonary edema and a third heart sound.
2. The **mechanical complications** of mitral regurgitation and ventricular septal defect are often heralded by a new systolic murmur (see Chapter 3). Early diagnosis of these complications relies on well-documented examination findings at baseline and during the hospital course.

V. DIFFERENTIAL DIAGNOSIS. The differential diagnosis of ST elevation includes conditions with comorbid ischemia such as acute aortic dissection involving the root, conditions with ST elevation but no ischemia such as left ventricular (LV) hypertrophy or early repolarization abnormality, and conditions with chest pain but no ischemia such as myopericarditis (Table 1.2). The most common differential diagnostic considerations are discussed in the following text.

A. Pericarditis. Chest pain that is worse when the person is supine and improves when the person is sitting upright or slightly forward is typical of pericarditis. Care must be taken in excluding acute MI, however, because pericarditis can complicate acute MI. The electrocardiographic abnormalities of acute pericarditis may also be confused with acute MI. Diffuse ST-segment elevation is the hallmark of acute pericarditis, but this finding may be seen in acute MI that involves the left main coronary artery or a large “wraparound” left anterior descending artery. PR-segment depression, peaked T waves, or electrocardiographic abnormalities out of proportion to the clinical scenario may favor the diagnosis of pericarditis. The ST-segment elevations in pericarditis are often concave, whereas the ST-segment elevations in acute MI are usually convex. Reciprocal ST depression does not occur in pericarditis, except in leads aVR and V₁. Early T-wave inversion is not a feature of acute pericarditis. Echocardiography may be useful, not in evaluating pericardial effusion, which may occur in either condition, but in documenting the lack of wall motion abnormalities in the setting of ongoing pain and ST elevation.

B. Myocarditis. As with pericarditis, the symptoms and electrocardiographic findings of myocarditis may be similar to those of acute MI. Echocardiography is less useful in differentiating this syndrome from acute MI, because segmental LV dysfunction may be encountered in either condition. A complete history often reveals a more insidious onset and associated viral syndrome with myocarditis.

TABLE 1.2 Differential Diagnostic Considerations for ST-Segment Elevation Myocardial Infarction

Comorbid ischemia	ST elevation but no ischemia	Chest pain but no ischemia
Aortic dissection	Early repolarization	Aortic dissection
Systemic arterial embolism	Left ventricular hypertrophy	Myopericarditis
Hypertensive crisis	Left bundle branch block	Pleuritis
Aortic stenosis	Hyperkalemia	Pulmonary embolism
Cocaine use	Brugada syndrome	Costochondritis
Arteritis		Gastrointestinal disorders

Adapted from Christofferson RD. Acute ST-elevation myocardial infarction. In: Shishehbor MH, Wang TH, Askari AT, et al., eds. *Management of the Patient in the Coronary Care Unit*. New York: Lippincott Williams & Wilkins; 2008.

- C. Acute aortic dissection.** Sharp, tearing chest pain that radiates through the chest to the back is typical of aortic dissection (see Chapter 26). This type of radiation pattern should be investigated thoroughly before administration of antithrombotic, antiplatelet, or fibrinolytic therapy. Proximal extension of the dissection into either coronary ostium can account for acute MI. A chest radiograph may reveal a widened mediastinum. Transthoracic echocardiography may reveal a dissection flap in the proximal ascending aorta. If it does not, a more definitive diagnosis should be obtained with transesophageal echocardiography (TEE), computerized tomography (CT), or magnetic resonance imaging (MRI).
- D. Pulmonary embolism.** Shortness of breath associated with pleuritic chest pain but without evidence of pulmonary edema suggests pulmonary embolism. Echocardiography helps to rule out wall motion abnormalities and may identify right ventricular (RV) dilatation and dysfunction in the setting of pulmonary embolism.
- E. Esophageal disorders.** Gastroesophageal reflux disease, esophageal motility disorders, and esophageal hyperalgesia can cause chest pain, the character of which is very similar to cardiac ischemic pain. These disorders can often coexist in patients with coronary disease, thereby complicating the diagnosis. A workup for coronary disease should precede evaluation of esophageal disorders. Symptoms that may be suggestive but not diagnostic of chest pain of an esophageal origin include postprandial symptoms, relief with antacids, and lack of radiation of pain.
- F. Acute cholecystitis** can mimic the symptoms and ECG findings of inferior acute MI, although the two can coexist. Tenderness in the right upper quadrant, fever, and an elevated leukocyte count favor cholecystitis, which can be diagnosed by means of hepatobiliary iminodiacetic acid (HIDA) scanning.

VI. LABORATORY EXAMINATION (Fig. 1.1)

- A. Troponins.** Troponin T and troponin I assays are particularly useful in the diagnosis and management of unstable angina and NSTEMI because of their high sensitivity, ability to be used and interpreted rapidly at bedside, and nearly universal availability. Currently, the lag time between occlusion and detectable elevations in serum levels limits their usefulness in the diagnosis of acute STEMI; however, the development of high-sensitivity troponin T assays may allow for more rapid detection of myocardial necrosis. Also, data have suggested that a single troponin T concentration measured 72 hours after acute MI may be predictive of MI size, independent of reperfusion (3). Troponin elevation in the absence of ischemic heart disease can be found in congestive heart failure (CHF), aortic dissection, hypertrophic cardiomyopathy, pulmonary embolism, acute neurologic disease, cardiac contusion, or drug toxicity.
- B. Creatine kinase (CK).** An elevated level of CK is rarely helpful in making the diagnosis of acute MI for a patient with ST-segment elevation. Because it usually takes 4 to 6 hours to see an appreciable rise in CK levels, an initial normal value does not exclude recent complete occlusion. CK and CK-MB (creatine kinase myocardial band) levels can be elevated in the presence of pericarditis and myocarditis, which may cause diffuse ST-segment elevation. CK levels are more helpful in gauging the size and timing of acute MI than in making the diagnosis. CK levels peak at 24 hours, but the peak CK level is believed to occur earlier among patients who undergo successful reperfusion. False-positive results of CK elevation occur in a variety of settings, including skeletal muscle disease or trauma (e.g., rhabdomyolysis).
- C. Myoglobin.** Damaged cardiac myocytes rapidly release this protein into the bloodstream. Peak levels occur between 1 and 4 hours, allowing for early diagnosis of acute MI. However, myoglobin lacks cardiac specificity, thereby limiting its clinical utility. Studies have indicated that it might play a role in risk stratification after reperfusion therapy (4).

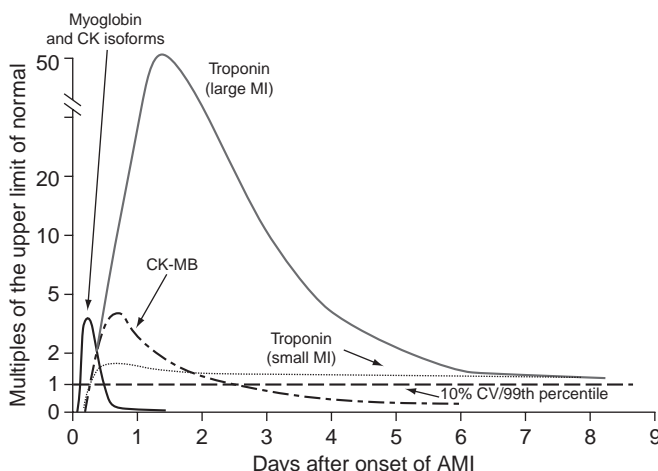


FIGURE 1.1 Timing of biomarker release after acute myocardial infarction. AMI, acute myocardial infarction; CK, creatine kinase; CK-MB, creatine kinase myocardial band; CV, coefficient of variation. (Reprinted from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction—executive summary. *J Am Coll Cardiol.* 2007;50:652–726, with permission from Elsevier.)

VII. DIAGNOSTIC TESTING

A. Electrocardiography

1. **Definitive electrocardiographic diagnosis** of acute MI requires ST elevation of 1 mm or more in two or more contiguous leads, often with reciprocal ST depression in the contralateral leads. In leads V_2 – V_3 , 2 mm of ST elevation in men and 1.5 mm in women are required for accurate diagnosis.
2. **ECG subsets.** ST-segment elevations can be divided into subgroups that may be correlated with the infarction-related artery and risk of death. These five subgroups are listed in Table 1.3 and illustrated in Figure 1.2.
3. **Left bundle branch block**
 - a. **New LBBB in the setting of symptoms consistent with acute MI** may indicate a large, anterior wall acute MI involving the proximal left anterior descending coronary artery and should be managed as acute STEMI.
 - b. **In the absence of an old ECG or in the presence of LBBB at baseline**, the diagnosis of acute STEMI can be made with > 90% specificity on the basis of the criteria listed in Table 1.4 and illustrated in Figure 1.3.
 - c. **Right bundle branch block (RBBB)** may complicate interpretation of ST elevation in leads V_1 through V_3 . RBBB does not, however, obscure ST-segment elevation.
4. **Echocardiography** may be helpful in the evaluation of LBBB of undetermined duration in that the lack of regional wall motion abnormality in the presence of continuing symptoms makes the diagnosis of acute MI unlikely. It is worth noting that abnormal septal motion is often observed in the setting of LBBB even in the absence of ischemia.

TABLE 1.3 Acute Myocardial Infarction: Electrocardiogram Subsets and Correlated Infarct-Related Artery and Mortality

Category	Anatomy of occlusion	ECG findings	30-Day mortality rate (%) ^a	1-Year mortality rate (%)
1. Proximal LAD	Proximal to first septal perforator	ST ↑ V ₁ –V ₆ , I, aVL and fascicular or bundle branch block	19.6	25.6
2. Mid-LAD	Proximal to large diagonal but distal to first septal perforator	ST ↑ V ₁ –V ₆ , I, aVL	9.2	12.4
3. Distal LAD or diagonal	Distal to large diagonal or diagonal itself	ST ↑ V ₁ –V ₆ , or I, aVL, V ₅ , V ₆	6.8	10.2
4. Moderate to large inferior (posterior, lateral, right ventricular)	Proximal RCA or left circumflex	ST ↑ II, III, aVF, and any of the following: (a) V ₁ , V ₃ R, V ₄ R (b) V ₅ , V ₆ (c) R > S in V ₁ , V ₂	6.4	8.4
5. Small inferior	Distal RCA or left circumflex branch	ST ↑ II, III, aVF only	4.5	6.7

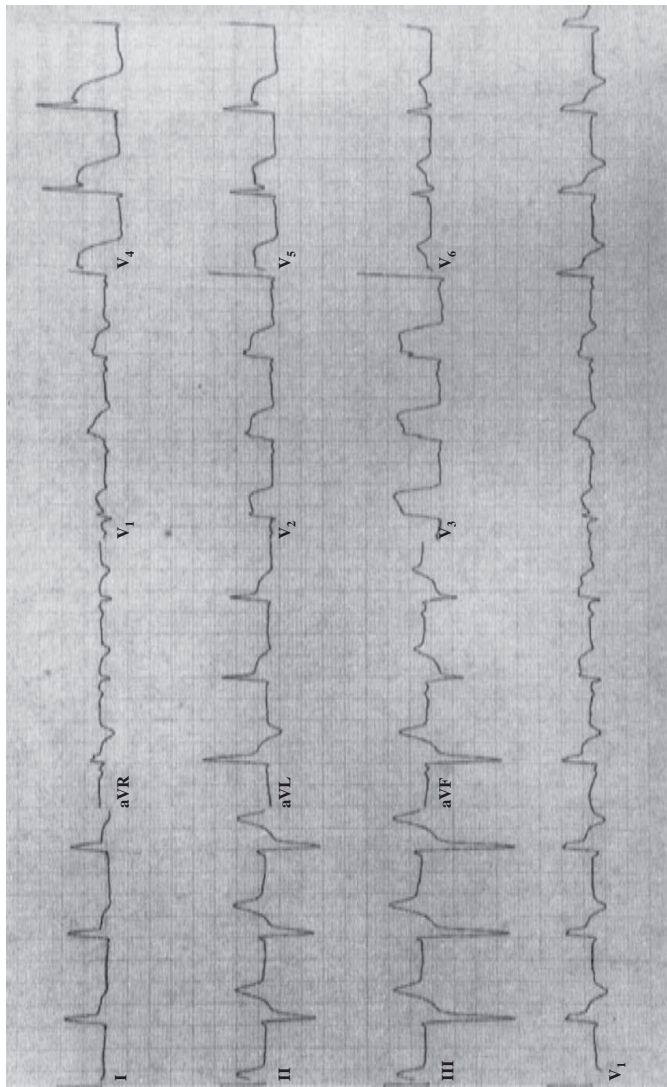
ECG, electrocardiogram; LAD, left anterior descending (coronary artery); ↑, increased; RCA, right coronary artery.

^aMortality rate based on GUSTO I cohort population in each of the 5 year categories, all receiving reperfusion therapy.

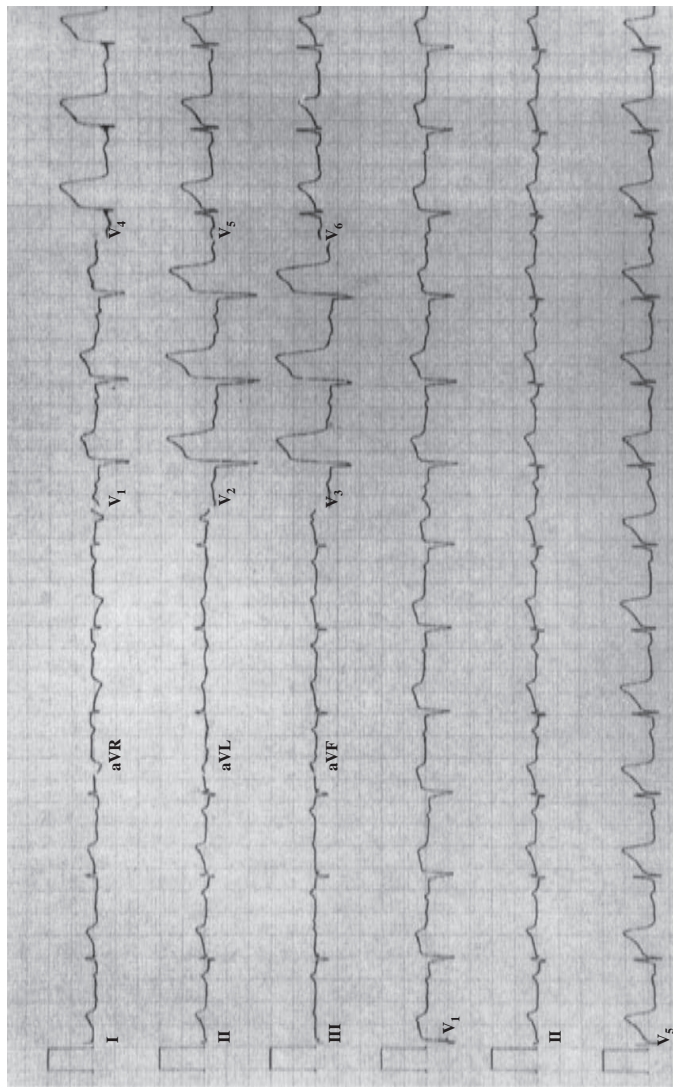
From Topol EJ, Van de Werf FJ. Acute myocardial infarction: early diagnosis and management. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. New York: Lippincott-Raven; 1998, with permission.

VIII. RISK STRATIFICATION. It is possible and useful to estimate the risk of death of a patient with acute MI. The estimate can aid in making treatment decisions and recommendations and in counseling patients and families. Five simple baseline parameters have been reported to account for > 90% of the prognostic information for 30-day mortality. These characteristics are given in descending order of importance: age, systolic blood pressure, Killip classification (Table 1.5), heart rate, and location of MI (Table 1.3, Fig. 1.2) (5). In addition, various risk models have been created to improve risk prediction.

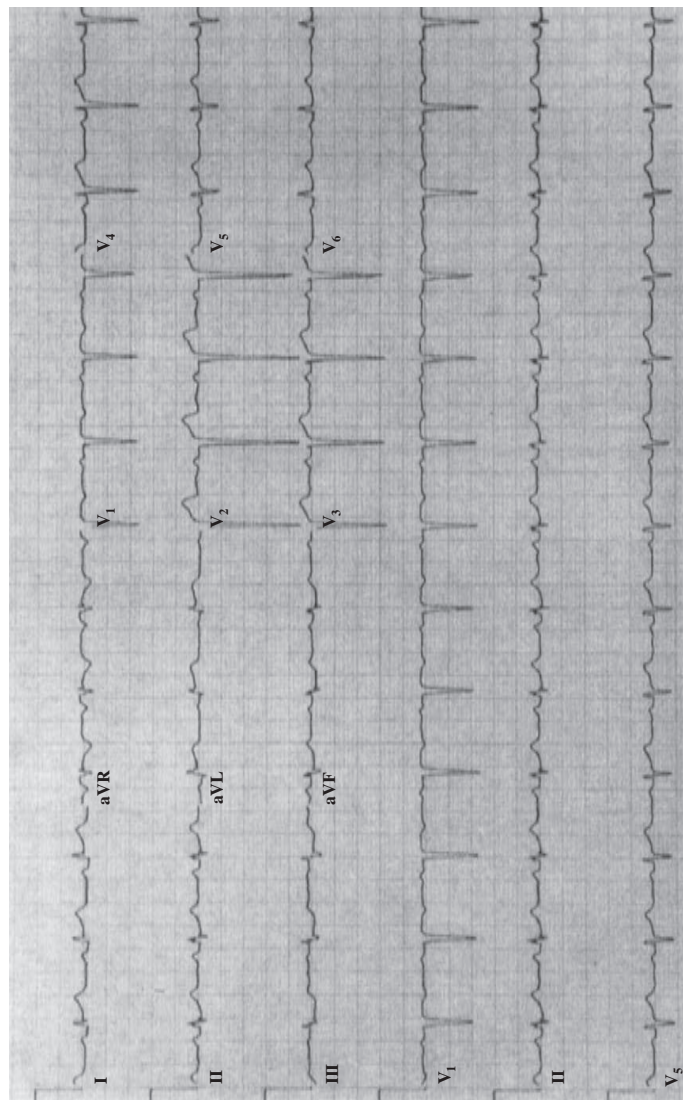
A. The Thrombolysis in Myocardial Infarction (TIMI) risk score incorporates eight variables obtained from the history, physical examination, and ECG (Table 1.6). In patients treated with fibrinolysis, a TIMI score of 9 or greater predicts a 30-day mortality of approximately 35%. In patients with a TIMI score of 0 or 1, the 30-day mortality rate is < 2%. The strongest predictor of poor prognosis is advanced age (where age ≥ 75 years receives 3 points and age 65 to 74 years receives 2 points). Other variables that predict a poor prognosis include hypotension, Killip class II–IV at presentation, tachycardia, history of diabetes or hypertension, anterior ST elevation (also complete LBBB), low body weight, and a time to treatment of > 4 hours.



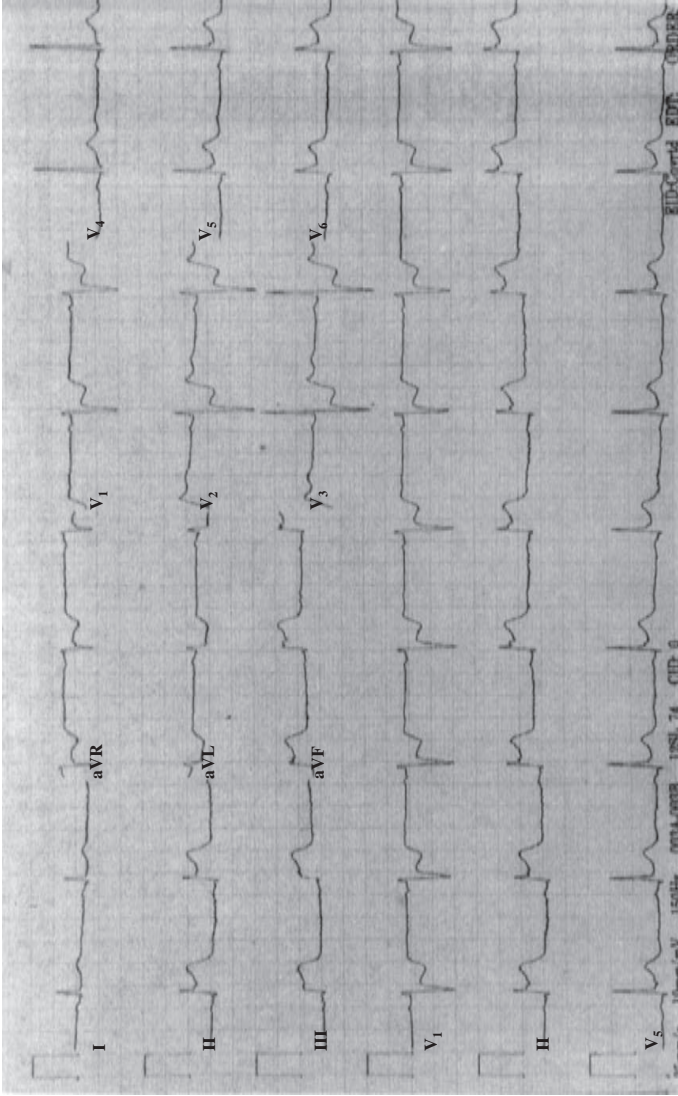
A



B



C



D

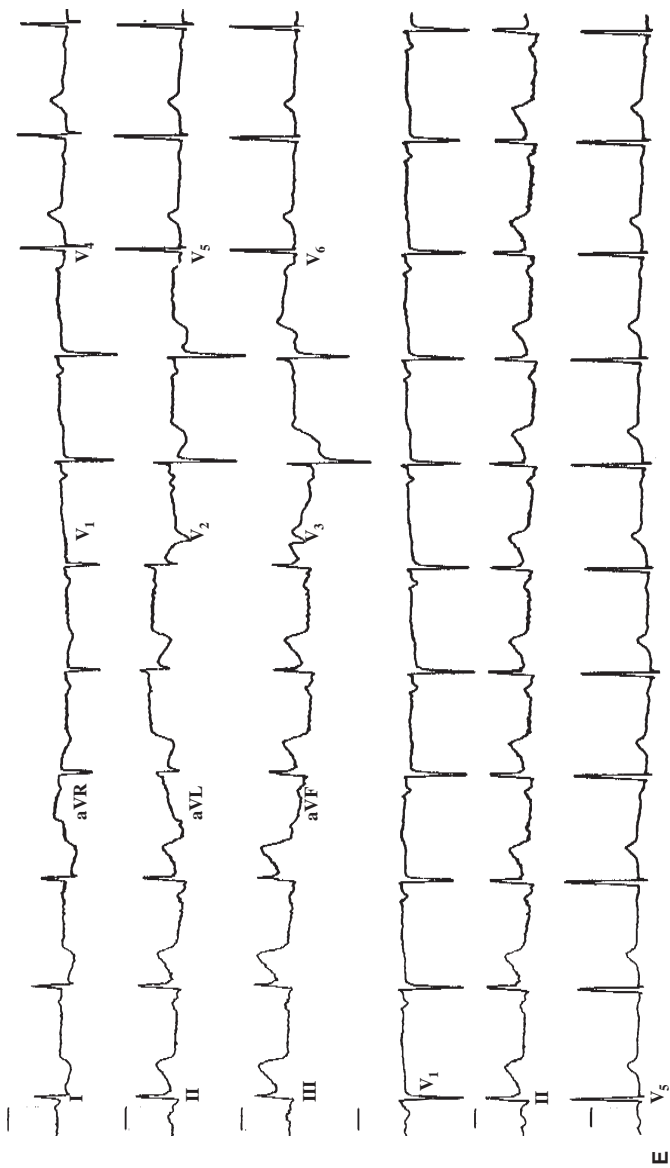


FIGURE 12 Electrocardiographic subsets of acute myocardial infarction (MI). **A:** Large anterior MI with conduction disturbance (proximal left anterior descending [LAD] coronary artery). **B:** Anterior MI without conduction disturbance (mid-LAD). **C:** Lateral MI (distal LAD, diagonal branch, or left circumflex branch). **D:** Large inferior MI with reciprocal changes (proximal right coronary artery [RCA]). **E:** Small inferior MI (distal RCA). (From Topol E.J. Van de Werf F.J. Acute myocardial infarction: early diagnosis and management. In: Topol E.J., ed. *Textbook of Cardiovascular Medicine*. New York: Lippincott-Raven; 2002, with permission).¹

TABLE 1.4 **Electrocardiographic Criteria for the Diagnosis of Acute Myocardial Infarction in the Presence of Left Bundle Branch Block**

Criterion	Score ^a
ST-segment elevation ≥ 1 mm concordant with QRS	5
ST-segment depression ≥ 1 mm in leads V_1 , V_2 , or V_3	3
ST-segment elevation ≥ 5 mm discordant with QRS	2

^aPoint scores for each criterion met are added. Total point score of 3 yields $\geq 90\%$ specificity and an 88% positive predictive value.

Adapted from Sgarbossa EB, Pinski SL, Barbagelata A, et al. Electrocardiographic diagnosis of evolving acute myocardial infarction in the presence of left bundle branch block. *N Engl J Med*. 1996;334:481–487.

- B. The Global Registry of Acute Coronary Events (GRACE) score** is used to predict in-hospital mortality in patients with ACS. Risk is calculated based on Killip class, heart rate, systolic blood pressure, creatinine level, age, presence or absence of cardiac arrest at admission, presence or absence of cardiac biomarkers, and ST-segment deviation. Patients with a score of ≤ 60 have a $\leq 0.2\%$ probability of in-hospital mortality, whereas patients with a score of ≥ 250 have a $\geq 52\%$ probability of in-hospital mortality.

IX. THERAPY

A. Prior to reperfusion

- 1. Aspirin.** Immediate administration of aspirin is indicated for all patients with acute MI, unless there is a clear history of true aspirin allergy (not intolerance). Aspirin therapy conveys as much mortality benefit as streptokinase (SK), and the combination provides additive benefit (6). The dose should be four 81 mg chewable tablets (for more rapid absorption) or one 325 mg nonchewable tablet. If oral administration is not possible, a rectal suppository can be given. If true aspirin allergy is present, clopidogrel monotherapy is the best alternative. In STEMI patients who undergo PCI, aspirin should be continued indefinitely. According to the 2011 ACCF/AHA/SCAI PCI guidelines, after PCI it is reasonable to use 81 mg of aspirin as opposed to higher maintenance doses (16).
- 2. Oxygen.** Supplemental oxygen by means of nasal cannula should be given to all patients with suspected MI. Administration through a face mask or endotracheal tube may be necessary for patients with severe pulmonary edema or cardiogenic shock.
- 3. Nitroglycerin.** It is worthwhile to give sublingual nitroglycerin (0.4 mg) to determine whether the ST-segment elevation represents coronary artery spasm while arrangements for reperfusion therapy are being initiated. Patients should be questioned about recent use of a phosphodiesterase inhibitor (PDE) because administration of nitroglycerin within 24 hours of a PDE may cause life-threatening hypotension. A meta-analysis performed before the age of routine reperfusion suggested a mortality benefit with intravenous nitroglycerin (8), although routine use of oral nitrates after MI had no benefit in two large randomized trials in the modern era. Nitroglycerin can be useful in the management of acute MI complicated by CHF, ongoing symptoms, or hypertension. A 30% reduction in systolic blood pressure can be expected with appropriately

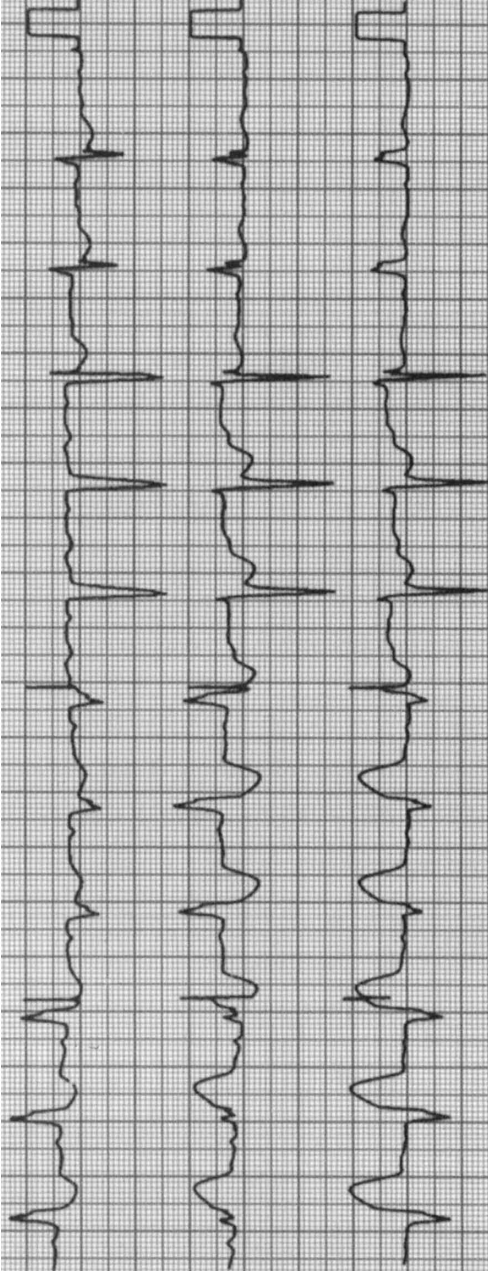


FIGURE 1.3 Electrocardiogram displays all of the criteria for the diagnosis of acute myocardial infarction (MI) in the setting of left bundle branch block (LBBB): ST-segment elevation > 1 mm, concordant with QRS in lead II (5 points); ST-segment depression > 1 mm in leads V_2 and V_3 (3 points); and ST-segment elevation > 5 mm, discordant with QRS in leads III and VF (2 points). A score of 10 points indicates an extremely high likelihood of inferior MI. (From Sgarbossa EB, Wagner G, 1997, with permission.)

TABLE 1.5 30-Day Mortality Based on Hemodynamic (Killip) Class

Killip class	Characteristics	Patients (%)	Mortality rate (%)
I	No evidence of CHF	85	5.1
II	Rales, ↑ JVD, or S ₃	13	13.6
III	Pulmonary edema	1	32.2
IV	Cardiogenic shock	1	57.8

CHF, congestive heart failure; ↑, increased; JVD, jugular venous distention; S₃, third heart sound.

Adapted from Lee KL, Woodlief LH, Topol EJ, et al. Predictors of 30-day mortality in the era of reperfusion for acute myocardial infarction. Results from an international trial of 41,021 patients. GUSTO-I Investigators. *Circulation*. 1995;91:1659-1668.

TABLE 1.6 TIMI Risk Model for Prediction of Short-Term Mortality in ST-Segment Elevation Myocardial Infarction Patients

History	
Age 65–74 years	2 points
Age ≥ 75 years	3 points
Angina or DM/HTN	1 point
Physical examination	
HR > 100 bpm	2 points
SBP < 100 mm Hg	3 points
Killip class II–IV	2 points
Weight < 67 kg	1 point
Presentation	
Anterior ST elevation or LBBB	1 point
Time to treatment > 4 h	1 point
TIMI risk score = total points (0–14)	

DM, diabetes mellitus; HR, heart rate; HTN, hypertension; LBBB, left bundle branch block; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction.

Adapted from Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an intravenous nPA for treatment of infarcting myocardium early II trial substudy. *Circulation*. 2000;102:2031-2037.

aggressive dosing (10 to 20 µg/min with 5 to 10 µg/min increases every 5 to 10 minutes). Intravenous therapy can be continued for 24 to 48 hours, after which time patients with heart failure or residual ischemia can transition to oral or topical therapy with an appropriate nitrate-free interval to avoid tachyphylaxis.

4. **Platelet P2Y₁₂ receptor antagonists** should be used routinely in all patients with STEMI regardless of whether or not PCI is performed (9). Currently, the three agents recommended for treatment of STEMI are clopidogrel, prasugrel, and ticagrelor. Clopidogrel and prasugrel are thienopyridines that irreversibly inhibit the platelet adenosine diphosphate P2Y₁₂ receptor, and Ticagrelor is a reversible direct inhibitor of this same receptor. In patients in whom PCI is planned, a loading dose should be given prior to or at the time of PCI. The recommended loading dose of clopidogrel is 600 mg. This is largely based on results of a meta-analysis that included more than 25,000 patients undergoing PCI. The meta-analysis demonstrated that when compared to 300 mg, a 600 mg clopidogrel loading dose reduces MACE without an increase in major bleeding. (10). The recommended loading dose of prasugrel is 60 mg (9). Prasugrel is considered to be superior to clopidogrel in onset of action and potency of platelet inhibition; in addition, its metabolism is not influenced by cytochrome P450 genetic polymorphisms. The TRITON-TIMI 38 (Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel–Thrombolysis In Myocardial Infarction) investigators compared efficacy and safety of prasugrel versus clopidogrel in patients with moderate- to high-risk ACS undergoing PCI. The primary end point was a composite of death due to cardiovascular causes, nonfatal MI, or nonfatal stroke. Patients who received prasugrel had a significant reduction in the primary end point compared with patients who received clopidogrel (9.9% vs. 12.1%; hazard ratio [HR] 0.81; 95% confidence interval [CI], 0.73 to 0.90; $p < 0.001$). This difference was primarily driven by a reduction in nonfatal MI (7.3% for prasugrel vs. 9.5% for clopidogrel; HR 0.76; 95% CI, 0.67 to 0.85; $p < 0.001$). The risk of TIMI major bleeding was higher with the use of prasugrel (2.4% vs. 1.8%; HR 1.32; 95% CI, 1.03 to 1.68; $p = 0.03$), though the net clinical benefit end point, which included all-cause mortality, ischemic events, and major bleeding events, still favored the use of prasugrel (11). Based on subgroup analysis, diabetics derived a greater benefit with prasugrel as compared with clopidogrel, whereas post hoc analysis showed that patients 75 years of age or older or patients with a body weight of < 60 kg derived no net clinical benefit from prasugrel. Post hoc analysis also showed net harm in patients treated with prasugrel who had a history of a transient ischemic attack or stroke, and therefore prasugrel should be avoided in these patients (11). Ticagrelor is given as a 180 mg loading dose. Platelet inhibition with ticagrelor occurs faster and is more potent than clopidogrel. The efficacy and safety of ticagrelor was compared to clopidogrel in the PLATO (Platelet Inhibition And Patient Outcomes) trial. At one year, patients who received ticagrelor had a significant reduction in the composite endpoint of death from vascular causes, MI, or stroke, without an increase in major bleeding. Of note, patients who receive ticagrelor should not be treated with high dose aspirin, which has been associated with worse outcomes in these patients (12). Currently, guidelines do not endorse one agent over another except in patients who have received fibrinolysis. In these patients, clopidogrel is the thienopyridine of choice, at a loading dose of 300 mg if fibrinolysis was performed within 24 hours of administration (13). This is based on results of the CLARITY-TIMI 28 (Clopidogrel as Adjunctive Reperfusion Therapy—Thrombolysis in Myocardial Infarction) trial, which showed pretreatment with clopidogrel to be safe and effective without increased bleeding among patients treated with fibrinolytic therapy, with many receiving subsequent PCI ($\sim 57\%$). The composite end point of cardiovascular death, reinfarction or revascularization, was reduced from 14.1% to 11.6% ($p = 0.03$) by clopidogrel pretreatment (9,13). In patients receiving a stent (BMS or drug-eluting stent [DES]), thienopyridine therapy should be continued for at least 1 year (9).

The maintenance dose of clopidogrel and prasugrel is 75 mg daily and 10 mg daily, respectively. The maintenance dose for prasugrel is 90 mg twice a day. An important consideration is the increased risk of major bleeding during surgery. It is currently recommended that clopidogrel and ticagrelor be held for 5 days and prasugrel be held for 7 days prior to CABG, unless the need for urgent revascularization outweighs the risk of potential excessive bleeding (9).

5. **Parenteral anticoagulants.** Unless there is a contraindication, all STEMI patients should receive antithrombotic therapy. Traditionally, this has been accomplished with unfractionated heparin (UFH). The dose of UFH is 60 U/kg as a bolus (maximum 4,000 U), followed by 12 U/kg/h infusion (maximum 1,000 U/h) to achieve a partial thromboplastin time of 45 to 65 seconds (7). Based on the GUSTO I (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) trial, heparin should be given as an adjunct to patients who receive thrombolysis with alteplase, but should not be given to patients who receive streptokinase unless the patient has recurrent ischemia or there is another indication for anticoagulant therapy (14). The use of UFH as adjunctive therapy with reteplase and tenecteplase (TNK) has been validated in GUSTO III and ASSENT 2 (Assessment of the Safety and Efficacy of a New Thrombolytic), respectively. Low-molecular-weight heparin (LMWH) is an alternative to UFH and should be preferred in patients undergoing fibrinolysis. The ASSENT 3 trial tested the efficacy of various antithrombotic regimens in conjunction with weight-based TNK. TNK plus enoxaparin was superior to TNK plus UFH in reducing the composite end point of death, in-hospital reinfarction, or in-hospital refractory ischemia (15). Similarly, the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment - Thrombolysis in Myocardial Infarction) trial randomized STEMI patients undergoing fibrinolysis to either enoxaparin throughout the index hospitalization or UFH for 48 hours. The primary end point was death or nonfatal MI at 30 days. The enoxaparin group had a significant reduction in the primary end point, most of which was due to a significant reduction in the rate of reinfarction (3.0% vs. 4.5%). The enoxaparin group was also less likely to undergo urgent revascularization (2.1% vs. 2.8%). It is worth noting that duration of therapy differed between the two groups. Although UFH was only administered for 48 hours, LMWH therapy was continued for a mean of 7 days (16). Patients undergoing PCI after treatment with LMWH may need additional dosing in the cardiac catheterization laboratory, depending on the time at which the last dose was administered. If the last dose was within 8 hours, no additional enoxaparin should be given. If the last dose was given 8 to 12 hours earlier, an intravenous dose of 0.3 mg/kg should be given. If it has been > 12 hours since that last dose, an additional 1 mg/kg dose should be administered subcutaneously. LMWH should be avoided in patients > 75 years old or in patients with significant renal insufficiency (22). The 2009 focused update of the ACC/AHA STEMI guidelines added bivalirudin as an acceptable anticoagulant in patients undergoing primary PCI (9). The 2011 ACCF/AHA/SCAI PCI guideline confirmed this with a class I recommendation for bivalirudin during PCI (17). This is primarily based on results of the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) trial. The HORIZONS-AMI trial randomized 3,600 patients to either bivalirudin and provisional glycoprotein (GP) IIb/IIIa inhibitor or UFH and planned GP IIb/IIIa inhibitor prior to primary PCI. The primary end point was the 30-day rate of the combined outcome of net adverse clinical events, including major bleeding, death, reinfarction, target vessel revascularization (TVR), and stroke. Patients in the bivalirudin group

had a significant reduction in the primary end point (9.2% vs. 12.1%; relative risk [RR] 0.76; 95% CI, 0.63 to 0.92; $p = 0.005$) primarily due to decreased major bleeding (4.9% vs. 8.3%; $p = 0.001$). The benefit was maintained at 1 year (18). Fondaparinux is a synthetic pentasaccharide factor Xa inhibitor that has also been studied in acute MI. The OASIS-6 (Organization for the Assessment of Strategies for Ischemic Syndromes) trial evaluated fondaparinux with fibrinolytics and appeared to demonstrate benefit versus placebo/UHF in terms of death and reinfarction at 30 days (9.7% vs. 11.2%; HR – 0.86; 95% CI, 0.77 to 0.98; $p = 0.008$) without an increased risk of bleeding (19). However, in the primary PCI subset, there was no benefit and a significant increase in guiding catheter thrombosis, which has limited its widespread use. Accordingly, current ACC/AHA guidelines recommend that patients treated with fondaparinux receive additional anticoagulation with an anti-IIa agent prior to proceeding with PCI.

B. Reperfusion therapy. The primary goal in the management of acute MI is to institute reperfusion therapy as quickly as possible. All patients with ST-segment elevation or new LBBB MI who seek treatment within 12 to 24 hours from onset of continuous symptoms should be considered for immediate reperfusion therapy. Persistent ischemic symptoms after 12 hours may indicate a stuttering course of occlusion, spontaneous reperfusion, and reocclusion and may indicate potential continued benefit for early therapy.

1. **Benefit.** The benefit of reperfusion therapy has been well documented in the management of acute MI, regardless of age, gender, and most baseline characteristics. However, the patients who derive the most benefit are those treated earliest and those at highest risk, such as those with anterior MI.
2. **Time to treatment is paramount.** Patients treated in the first hour have the highest mortality benefit. **There is an inverse relationship between time to treatment and survival benefit.** This relationship appears more consistent with fibrinolytic therapy than with direct PCI. After 12 hours of continuous symptoms, there is little net benefit to pharmacologic reperfusion with fibrinolytics. The therapeutic window for PCI extends beyond that of fibrinolysis, but is not infinite (20,21). The Occluded Artery Trial (OAT) suggests that stenting of an occluded infarct-related artery > 72 hours after the initial event is not associated with benefit and may be harmful (21). Currently, the AHA recommends against PCI of an occluded infarct-related artery > 24 hours after STEMI if the patient is hemodynamically stable and does not have signs of severe ischemia (22).
3. **Fibrinolysis versus direct PCI.** After it has been determined that a patient is a candidate for reperfusion therapy, the decision to use fibrinolytic or direct PCI therapy must be made quickly.
 - a. If facilities for immediate coronary angiography and PCI are available within 90 minutes of first medical contact, this is the preferred therapy. Pooled data from several large trials show a significant (22%) reduction in short-term mortality for patients treated with primary angioplasty (23). This benefit was durable because there were significant reductions in the incidence of death, nonfatal MI, and recurrent ischemia at long-term follow-up. PCI is also associated with a reduction in the incidence of intracerebral hemorrhage compared with fibrinolytic therapy.
 - b. If facilities for immediate coronary angiography and direct PCI are not available, fibrinolytic therapy, unless contraindicated, should be instituted within 30 minutes of first medical contact. There is some controversy regarding the use of primary PCI with prolonged transfer times. Several trials, including the DANAMI-2 (Danish Multicenter Randomized Study on Thrombolytic Therapy Versus Acute Coronary Angioplasty in Acute Myocardial Infarction) (24), the Air-PAMI (Air-Primary Angioplasty in

Myocardial Infarction) (25), and the PRAGUE (Primary Angioplasty in Patients Transferred from a General Community Hospital to Specialized PTCA Units) (26), have investigated the benefit of on-site fibrinolysis compared with transfer to tertiary centers for direct PCI. These studies have found improved outcomes in patients randomized to a transfer strategy and direct PCI even after taking into account the increased time for patient transfer. For example, patients in DANAMI-2 randomized to transfer for PCI had a significantly lower 30-day incidence of death, MI, or stroke (8.5% vs. 14.3%; $p = 0.002$) despite a median time from randomization to balloon inflation of 112 minutes. According to current guidelines, if a patient presents with STEMI at a PCI-capable facility and can undergo PCI within 90 minutes of first medical contact, this is the preferred approach. Conversely, if the patient presents to a hospital without PCI capability and cannot receive PCI within 120 minutes of first medical contact, fibrinolytics should be administered within 30 minutes of hospital presentation (17,22). This assumes that there are no contraindications to fibrinolysis (Table 1.7).

- c. If a contraindication to fibrinolytic therapy exists or there is some question of the diagnosis, arrangements should be made for transfer to a PCI facility.

TABLE 1.7 **Contraindications and Cautions for Use of Thrombolytic Agents to Manage Myocardial Infarction**

Absolute contraindications

Previous hemorrhagic stroke at any time; ischemic stroke within 3 mo
 Known intracranial neoplasm, structural cerebral vascular lesion, or closed head injury within 3 mo
 Active bleeding or bleeding diathesis (excluding menses)
 Suspected aortic dissection

Relative contraindications

Severe, uncontrolled hypertension at presentation (blood pressure > 180/110 mm Hg) or history of chronic severe hypertension
 History of ischemic stroke > 3 mo, dementia, or known intracerebral pathologic condition not covered in contraindications
 Current use of anticoagulants, the risk increases with increasing INR
 Traumatic or prolonged (> 10 min) CPR or major surgery (< 3 wk)
 Noncompressible vascular punctures
 Recent (within 2–4 wk) internal bleeding
 For streptokinase or anistreplase: prior exposure (> 5 d prior) or prior allergic reaction
 Pregnancy
 Active peptic ulcer

CPR, cardiopulmonary resuscitation; INR, international normalized ratio.

Adapted from Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). *J Am Coll Cardiol.* 2004;44:E1–E211.

- d. Because of the relative lack of efficacy of lytic therapy among patients with cardiogenic shock or prior bypass operations, such patients are especially well suited for primary PCI.
4. **Primary PCI.** Once the decision has been made to perform reperfusion with primary PCI, the patient should be moved to the cardiac catheterization laboratory and undergo angiography as rapidly as possible. After the culprit lesion has been identified, reperfusion should be achieved with standard PCI techniques (see Chapter 65).
 - a. **Platelet GP IIb/IIIa inhibitors.** Several clinical trials, including RAPPORT (ReoPro and Primary PTCA Organization and Randomized Trial) and ADMIRAL (Abciximab before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long-Term Follow-up), have documented the benefits of abciximab in improving clinical outcomes after primary PCI with or without stenting in patients with STEMI (27,28). Despite these trials, the emergence of potent platelet ADP P2Y₁₂ receptor inhibitors has sparked controversy regarding the benefit of GP IIb/IIIa treatment in STEMI patients receiving dual, oral antiplatelet therapy. Three major trials have evaluated the efficacy of GP IIb/IIIa therapy in STEMI patients receiving dual, oral antiplatelet therapy. The Bavarian Reperfusion Alternatives Evaluation-3 (BRAVE-3) study looked at 800 STEMI patients who received aspirin plus 600 mg of clopidogrel and either abciximab or placebo during PCI. The primary end point was infarct size measured by single photon emission computed tomography prior to hospital discharge. The study also compared 30-day major adverse cardiovascular events (MACE) between the two groups. Compared with placebo, abciximab offered no additional benefit in terms of reducing infarct size or MACE (28,29). On-TIME 2 was a randomized control trial in Europe that compared outcomes in STEMI patients undergoing PCI who were treated with aspirin and 600 mg of clopidogrel plus either high-dose tirofiban or placebo. Patients in the high-dose tirofiban group had improved ST-segment resolution at 1 hour, but there was no significant difference in TIMI grade 3 flow or 30-day MACE (30). Lastly, in the HORIZONS-AMI trial, patients undergoing primary PCI for STEMI were randomized to either UFH plus a GP IIb/IIIa or bivalirudin with provisional GP IIb/IIIa therapy. All patients received aspirin and thienopyridine therapy prior to PCI. At 30 days, net adverse clinical events were higher in patients treated with a GP IIb/IIIa, primarily due to increased bleeding (18).

The timing of GP IIb/IIIa therapy has also been questioned. The FINESSE (Facilitated Intervention with Enhanced Speed to Stop Events) trial compared half-dose reteplase with abciximab, abciximab alone, or placebo (primary PCI) in patients undergoing PCI for STEMI. Although more patients with fibrinolytic plus GP IIb/IIIa therapy had an open artery on arrival to the catheterization laboratory, the composite primary end point of death or complications of MI at 90 days was no different among the various strategies (9.8% half-dose fibrinolytic + GP IIb/IIIa inhibitor, 10.5% GP IIb/IIIa inhibitor alone, and 10.7% placebo; $p = \text{NS}$), suggesting no benefit to upstream GP IIb/IIIa therapy (31). In addition, bleeding rates were higher with half-dose fibrinolytic + GP IIb/IIIa inhibitor (31).

Meta-analyses have been performed to compare the efficacy of small molecule GP IIb/IIIa inhibitors with abciximab in STEMI patients undergoing PCI. Results show no statistically significant difference in 30-day mortality, reinfarction, major bleeding, TIMI grade 3 flow, or ST-segment resolution between eptifibatide, tirofiban, and abciximab (32,33).

Based on all available data, if a patient has no contraindication to dual, oral antiplatelet therapy, it is reasonable to reserve the use of GP IIb/IIIa

therapy until coronary anatomy has been defined. Current ACC/AHA guidelines reflect this practice, as GP IIb/IIIa administration during PCI carries a class IIa recommendation, while upstream use is classified as class III (17). Also according to current guidelines, abciximab, tirofiban, and eptifibatide are considered equivalent options for GP IIb/IIIa therapy in patients undergoing PCI for STEMI (9).

- b. Thrombus aspiration.** The use of aspiration catheters has been shown to improve ST-segment resolution and myocardial blush and more recently has been associated with improved clinical outcomes. TAPAS (Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study) was a single-center, randomized, clinical trial that compared manual thrombus aspiration before PCI with conventional balloon angioplasty and stenting in patients with STEMI (34). Unless contraindicated, all patients were treated with aspirin, 600 mg of clopidogrel, UFH, and abciximab. Complete resolution of ST-segment elevation occurred in significantly more patients who received aspiration thrombectomy when compared with patients who underwent conventional balloon angioplasty and PCI (56.6% vs. 44.2%; $p < 0.001$). In addition, a TIMI myocardial blush grade of 0 or 1 occurred in 17.1% of patients who received aspiration thrombectomy compared with 26.3% of patients who received conventional PCI ($p < 0.001$) (34). Although death, reinfarction, and TVR rates did not differ at 30 days, at 1 year there was a significant reduction in the rates of cardiac death (3.6% vs. 6.7%; $p = 0.02$) and cardiac death or nonfatal reinfarction (5.6% vs. 9.9%; $p = 0.009$) in the thrombus aspiration group (34,35). Based on current guidelines, thrombus aspiration is considered reasonable during PCI in patients with STEMI who have a high clot burden and short ischemic times (9).
- c. Distal embolic protection devices (EPDs)** have failed to show any benefit in multiple trials and may in fact increase infarct size. The major criticism of these trials is the exclusion of patients with large thrombus burden. Regardless of this caveat, these devices are not routinely recommended for acute PCI of native coronary arteries. If the culprit vessel is a saphenous vein bypass graft, an EPD should be used, as it has been shown to reduce a 30-day composite outcome of death, MI, emergency CABG, and target-lesion revascularization (TLR).
- d. Coronary stenting.** The early benefit of angioplasty over thrombolytic therapy is attenuated with more extended follow-up. In the GUSTO IIb expanded previously trial in which use of accelerated tissue plasminogen activator (tPA) was compared with angioplasty alone (percutaneous transluminal coronary angioplasty, PTCA), the reduction in rates of death and nonfatal MI at 30 days (13.7% tPA vs. 9.6% PTCA) dwindled, and by 6 months, the difference (16.1% for tPA vs. 14.1% for PTCA) had lost statistical significance (36). This loss of effect may be at least partially caused by restenosis of the target lesion that was managed directly with angioplasty. Although coronary stents are known to reduce rates of restenosis during elective PCI, it was once believed that stents should not be placed in thrombus-laden lesions, such as those associated with acute MI, because of risk of in-stent thrombosis. However, clinical trials with adequate antiplatelet therapy have shown stenting to be safe. The STENT-PAMI (STENT-Primary Angioplasty in Myocardial Infarction) (37) study found that coronary stenting significantly reduced the need for TVR at 6 months (7.7% vs. 17.0%; $p < 0.001$). These findings were confirmed in the CADILLAC (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications) (38) trial, which found that coronary stenting significantly reduced the incidence of restenosis at 6 months (40.8% vs. 22.2%; $p < 0.0001$),

independent of abciximab use. Based on several meta-analyses, there does not appear to be a difference between DES and BMS in terms of mortality, MI, or risk of stent thrombosis (39–41). There is, however, a reduction in TVR with DES (39–41). This was also seen in the HORIZONS-AMI trial, which randomized > 3,000 patients to DES or BMS in a 3:1 ratio. At 12 months, there was no difference in the composite end point of death, reinfarction, stroke, or stent thrombosis; however, DES patients had a decreased rate of ischemia-driven TVR and TLR (5.8% vs. 8.7% and 4.5% vs. 7.5%, respectively) (18,42). Accordingly, patients with the highest risk of in-stent restenosis such as diabetics and patients with long, smaller diameter coronary lesions derive the greatest benefit from DES. In 2009, the ACC/AHA guidelines were updated to include DES as an alternative to BMS in patients undergoing primary PCI for STEMI (9). As mentioned by the ACC/AHA writing group members, the greatest challenge in determining if a STEMI patient is a candidate for DES is deciding in an emergent situation if the patient is a candidate for prolonged dual-antiplatelet therapy. The ideal candidate for a DES should not have social or financial barriers to prolonged dual-antiplatelet therapy, should have no surgical procedures scheduled within the next year, and should be at low risk for bleeding complications (9).

5. **Fibrinolytic therapy.** The lifesaving capability of early fibrinolytic therapy has been well established, beginning with the GISSI 1 (Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico) trial (43) in 1986. Pooled data show a relative reduction in mortality of 18% and an absolute reduction of nearly 2%. Even more dramatic long-term mortality benefit may be the result of preservation of normal LV function.

- a. **Contraindications.** As discussed previously (Table 1.7), the only **absolute contraindications to fibrinolytic therapies are recent cerebrovascular accident (CVA), hemorrhagic CVA, intracranial neoplasm, active internal bleeding, and suspected aortic dissection.** The presence of one of these or one or more of the relative contraindications would favor PCI, even if it meant delaying reperfusion.

- b. **Choice of agent**

- (1) **Alteplase (tPA).** The GUSTO I previously expanded trial showed that use of accelerated alteplase significantly reduced 30-day mortality rate by 15% relative to SK plus subcutaneous or intravenous heparin (14). This mortality reduction correlated with significantly higher rates of TIMI 3 flow at 90 minutes compared with SK (54% vs. 31%; $p < 0.001$). The benefit was initially challenged because of the high cost of alteplase (approximately US \$2,200 per episode of MI) compared with SK (approximately US \$300). For alteplase, this corresponds to a cost of US \$32,678 per year of life saved, less than that of the well-accepted standard of hemodialysis for end-stage renal disease (44). The benefit was seen across all subgroups, although the patients at highest risk derived the most benefit. The accelerated protocol consisted of an intravenous bolus dose of 15 mg followed by 0.75 mg/kg (up to 50 mg) over 30 minutes and then 0.5 mg/kg over 60 minutes. Alteplase is considered a fibrin-specific agent because of its relative selectivity for clot-bound fibrin.

- (2) **Retepase.** The first of the third-generation fibrinolytic agents approved for use in the United States, reteplase, is a less fibrin-specific mutation of alteplase. Reteplase has a longer half-life than alteplase and can be administered in a double bolus (10 mg each, 30 minutes apart). The GUSTO III trial (45) showed no mortality benefit of reteplase over alteplase, but its ease of use may help to reduce time to administration.

- (3) **Tenecteplase**, another third-generation fibrinolytic, is characterized by its improved fibrin specificity, enhanced resistance to plasminogen activator inhibitor 1, and decreased plasma clearance. These properties allow it to be administered as a single bolus. The ASSENT 2 trial found no mortality difference between TNK and tPA at 30 days (46). However, TNK was associated with significantly less noncerebral bleeding and improved mortality in patients treated for > 4 hours after symptom onset. The weight-adjusted dose of TNK is 30 to 40 mg (ASSENT 1).
- (4) **Streptokinase**. This first-generation nonfibrin-specific lytic is a reasonable alternative to second- or third-generation agents if newer agents are not available or cannot be used because of limited financial resources. Because of the possible development of antibodies, SK should not be administered to a patient who has received it in the past. Because the overall rate of intracerebral hemorrhage is lower with SK (0.5%) than with tPA (0.7%), some cardiologists advocate its use in the care of high-risk patients, such as elderly patients with a history of a cerebrovascular event or severe hypertension. SK is a nonfibrin-specific agent capable of lysing circulating and clot-bound plasminogen to plasmin. This process results in substantial systemic fibrinogenolysis, fibrinogenemia, and elevation in fibrin degradation products.
- c. **Bleeding complications after fibrinolysis.** The most serious **complication** of fibrinolytic therapy is **intracerebral hemorrhage, which occurs in approximately 0.5% to 0.7% of patients receiving such therapy. The major risk factors for intracranial hemorrhage include age (> 75 years), hypertension, low body weight, female gender, and coagulopathy** (e.g., prior Coumadin use). The diagnosis must be considered if a patient has severe headache, visual disturbances, new neurologic deficit, acute confusional state, or seizure. If the clinical suspicion is high, fibrinolytic, anti-thrombin, and antiplatelet therapy should be interrupted while emergency CT or MRI is performed and neurosurgical consultation is obtained. Surgical evacuation may be lifesaving. Even with prompt recognition and treatment, the mortality rate is higher than 60%; elderly patients (> 75 years) have a mortality rate higher than 90%. There is controversy regarding the risk of fibrinolytic therapy in elderly patients. An observational study (47) from the Medicare database found that patients older than 75 years had an increased risk of death at 30 days with fibrinolytic therapy (RR = 1.38; 95% CI, 1.12 to 1.71; $p = 0.003$). However, an updated meta-analysis of nine randomized trials (48,49) found that the risk reduction with fibrinolysis in patients older than 75 years was 16% (odds ratio = 0.84; 95% CI, 0.72 to 0.98; $p < 0.05$). There appears to be a decreasing relative benefit with fibrinolysis in the elderly, but an absolute gain in lives saved. The only randomized trial to specifically study management of STEMI in the elderly found that patients treated with PCI had significantly lower 30-day and 1-year mortality rates than patients treated with fibrinolysis (49). However, the ExTRACT-TIMI 25 study more recently indicates that fibrinolytic therapy may be safe in the elderly if a reduced dose of enoxaparin is used (16). Gastrointestinal, retroperitoneal, and access site bleeding may complicate fibrinolytic therapy but are usually not life-threatening if promptly recognized and managed. In any case, the best treatment of acute STEMI in elderly patients appears to be primary PCI.
- d. **Prehospital fibrinolysis.** Early administration of fibrinolytic therapy by emergency services has been shown to potentially reduce infarct size but lacks solid randomized trial data advocating its routine use. It has also been found to reduce time to treatment (50,51), but this did not translate

into a reduction in mortality. Although a meta-analysis (52) of prehospital fibrinolytic trials did find a 17% reduction of in-hospital mortality, it remains to be seen whether this strategy can improve long-term outcomes in clinical practice.

6. Combination fibrinolytic therapy with GP IIb/IIIa inhibitors (without PCI)

- a. Rationale.** Sustained tissue-level reperfusion occurs in only 25% of patients treated with fibrinolytic therapy. Platelets have paradoxically increased activity after fibrinolysis and are important mediators in the tendency for vessel reocclusion. Aspirin is pathway specific and, therefore, a relatively weak antiplatelet agent. GP IIb/IIIa inhibitors, however, are potent antiplatelet agents that block the final common pathway of platelet aggregation, and for this reason, they have been studied in combination with half-dose fibrinolysis.
- b. Clinical trials.** GUSTO V found that the addition of abciximab to half-dose reteplase did not reduce mortality at 30 days or 1 year compared with full-dose reteplase, but it did reduce reinfarctions and complications after MI (53). ASSENT 3 also found comparable reductions in reinfarction with the combination of half-dose TNK and abciximab (15).
- c. Contraindications.** GUSTO V found that the rate of intracranial hemorrhage in elderly patients (> 75 years) treated with combination therapy was almost twice that of standard lytic therapy (2.1% vs. 1.1%; $p = 0.07$). ASSENT 3 confirmed this finding. Age older than 75 years is, therefore, an additional contraindication for combination lytic therapy. No increase in intracranial hemorrhage was seen in younger patients.

7. Rescue percutaneous revascularization is defined as the use of PCI when fibrinolytic therapy has proved unsuccessful. Despite the proven mortality benefit, > 30% of patients who received lytic therapy have TIMI 0 to 1 flow at 90 minutes, whereas patency at 90 minutes has been shown to correlate with long-term survival (54). If reperfusion is not clearly evident 90 minutes after initiation of lytic therapy, particularly among patients with large acute MI, the decision to perform emergency angiography and mechanical reperfusion should be made promptly. Patients in cardiogenic shock, with severe CHF, or with compromising arrhythmias after lytic therapy should undergo immediate coronary angiography and should not await clinical assessment of reperfusion.

- a. Clinical determination of successful reperfusion.** It can be difficult to determine clinically whether a patient has successful reperfusion with fibrinolytic therapy. Resolution of chest pain is an inaccurate measure of reperfusion, because the pain may be blunted by narcotic analgesia or the partial denervation that is known to occur among some patients with MI. Serial assessment of 12-lead ECGs is a more reliable indicator of reperfusion, although it is also suboptimal. An accelerated idioventricular rhythm (AIVR) is fairly specific for reperfusion, but arrhythmias other than AIVRs are not reliable indicators because a variety of ventricular and supraventricular arrhythmias may be observed in patients with nonreperfused infarction-related artery. The complete resolution of chest pain and electrocardiographic changes (defined as > 70% resolution of ST-segment elevation), accompanied by a run of AIVR, is highly specific for successful reperfusion, but it occurs in < 10% of patients receiving lytic therapy. Resolution of ST-segment elevation by > 70% is correlated with effective tissue-level reperfusion, and this finding has been correlated with better clinical outcomes and angiographic reperfusion.
- b. Benefit.** It has been shown in the RESCUE (Randomized Evaluation of Salvage Angioplasty with Combined Utilization of Endpoints) trial (55) that patients with anterior MI who have unsuccessful thrombolysis (TIMI 0 or

1 flow) have a significant benefit from rescue angioplasty. In addition, the Rapid Early Action for Coronary Treatment (REACT) trial demonstrated that among patients with failed reperfusion with lytics, treatment with rescue angioplasty with or without PCI is associated with an ~50% reduction in death, reinfarction, stroke, and severe heart failure (56). The Grupo de Análisis de la Cardiopatía Isquémica Aguda I (GRACIA I) trial evaluated an early invasive strategy (within 24 hours) versus an ischemia-guided approach among patients with STEMI treated with fibrinolytic therapy. This trial primarily demonstrated a reduction in revascularization events with the early invasive approach, although a trend was seen toward fewer deaths and reinfarcts. Based on the above data, an early angiography strategy (within 24 hours) may also be considered a reasonable approach in all patients who receive lytic therapy. However, this approach should be differentiated from the facilitated PCI strategy described later.

8. **Facilitated PCI** refers to the use of an initial pharmacologic regimen to improve vessel patency rates prior to planned PCI. This method has been proposed as a way to manage patients with acute MI who present to hospitals without 24-hour catheterization laboratory facilities. Various facilitated PCI strategies have been proposed, including high-dose heparin, early GP IIb/IIIa inhibitors, full-dose or reduced-dose fibrinolytics, and combination fibrinolytics and GP IIb/IIIa inhibitors. Theoretical advantages include earlier time to reperfusion, improved hemodynamic stability, smaller infarct size, greater procedural success, and improved survival, albeit at increased risk for bleeding complications. The ASSENT 4 PCI previously expanded trial was the largest study to evaluate full-dose fibrinolytic therapy (TNK) plus PCI versus primary PCI alone. The trial was terminated prematurely because of higher in-hospital mortality rates (6% vs. 3%; $p = 0.01$) and higher primary composite end points (death, shock, and heart failure within 90 days) with full-dose fibrinolytics plus PCI versus primary PCI alone (18.6% vs. 13.4%; $p = 0.0045$) (57). As discussed previously, the FINESSE trial randomized STEMI patients undergoing PCI to half-dose reteplase with abciximab, abciximab alone, or placebo (primary PCI). Although more patients with fibrinolytic plus GP IIb/IIIa inhibitor had an open artery on arrival to the catheterization laboratory, the composite primary end point of death or complications of MI at 90 days was no different among the various strategies (9.8% half-dose fibrinolytic + GP IIb/IIIa inhibitor, 10.5% GP IIb/IIIa inhibitor alone, and 10.7% placebo; $p = \text{NS}$), the bleeding rates being higher with the half-dose fibrinolytic plus GP IIb/IIIa inhibitor. Finally, a large meta-analysis of multiple smaller trials confirmed that primary PCI is superior to facilitated PCI (58).
9. **Pharmacoinvasive Strategy.** Though it is clear that routine fibrinolysis prior to transfer for PCI in all patients who present with AMI (facilitated PCI) results in worse outcomes, fibrinolysis is still necessary to achieve early reperfusion in some patients who present to non-PCI-capable facilities. More recent data suggest that high risk patients (Table 1.8) who receive fibrinolytic therapy benefit from immediate transfer for PCI. The CARESS-in-AMI (Combined Abciximab REteplase Stent Study in Acute Myocardial Infarction) trial (59) randomized patients presenting to a non-PCI-capable facility, who received half-dose fibrinolytics and abciximab, to either immediate transfer for PCI or rescue PCI. Patients who were transferred immediately for PCI had a significant reduction in the primary endpoint of death, reinfarction, or refractory ischemia at 30 days (59). In addition, the TRANSFER-AMI (Trial of Routine Angioplasty and Stenting after Fibrinolysis to Enhance Reperfusion in Acute Myocardial Infarction) study showed that high-risk patients benefit from this pharmacoinvasive strategy. This trial looked at 1,059 high-risk patients with STEMI who presented to a non-PCI-capable facility within 12 hours of symptom onset (60). All patients

received fibrinolysis with TNK and were then randomized to immediate transfer for PCI or rescue PCI dictated by continued chest pain, < 50% resolution of ST elevation, or hemodynamic instability. The primary end point was 30-day composite of the first occurrence of death, MI, recurrent ischemia, new or worsening heart failure, and cardiogenic shock. The primary end point was significantly less common in the pharmacoinvasive group compared with the group who received rescue PCI (11% vs. 17.2%; RR 0.64; 95% CI, 0.47 to 0.87; $p = 0.004$) (60). Based on the CARESS-in-AMI and TRANSFER-AMI trials, the ACC/AHA now recommends abandoning the use of the terms “facilitated” and “rescue” and rather decide on transfer for PCI based on the patient’s level of risk (9). High-risk patients (Table 1.8) who receive fibrinolysis as the primary reperfusion strategy should be transferred to a PCI-capable facility as soon as possible. PCI can then be performed immediately or as needed. For low-risk patients, this management strategy is a class IIb recommendation (9).

10. **The late open artery hypothesis** postulates that benefit in terms of improved ventricular function, increased electrical stability, and provision of collaterals can be gained by late patency of occluded infarct arteries. However, OAT failed to show benefit of angioplasty for late total occlusion within 3 to 28 days after MI (21). Criticism of this trial includes exclusion of high-risk patients with New

TABLE 1.8 ACC/AHA Definition of High-Risk Patients with Acute Myocardial Infarction

Defined in CARESS-in-AMI

- (1) STEMI patients with one or more of the following:
 - Extensive ST-segment elevation
 - Previous MI
 - New-onset LBBB
 - Killip class > II or EF ≤ 35% for inferior MI
- (2) Anterior MI with ≥ 2 mm or more ST elevation in two or more leads

Defined in TRANSFER-AMI

- (1) ≥ 2 mm ST elevation in two anterior leads or ST elevation ≥ 1 mm in inferior leads with at least
 - SBP < 100 mm Hg
 - HR > 100 bpm
 - Killip class II–III
 - ≥ 2 mm ST-segment depression in anterior leads
 - ≥ 1 mm of ST elevation in right-sided lead V_4 indicative of RV infarct

EF, ejection fraction; HR, heart rate; LBBB, left bundle branch block; MI, myocardial infarction; RV, right ventricular; SBP, systolic blood pressure; STEMI, ST-segment elevation myocardial infarction; UFH, unfractionated heparin.

Adapted from Kushner FG, Hand M, King SB, et al. 2009 focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update). *J Am Coll Cardiol.* 2009;54:2205–2241.

York Heart Association (NYHA) class III or IV heart failure, rest angina, clinical instability, multivessel disease (left main or three-vessel disease), or severe inducible ischemia on stress testing. Regardless of these concerns, this study has led to a new **class III recommendation against PCI of a totally occluded artery > 24 hours after STEMI in asymptomatic patients without the previously noted high-risk criteria** (22).

11. **Emergency coronary bypass surgery** may be the treatment of choice for patients in whom the intent is to perform direct or rescue percutaneous mechanical reperfusion but who are found to have a critical left main stem lesion or severe three-vessel disease unapproachable with percutaneous revascularization. Studies of this strategy are fairly encouraging, especially when patients can be taken to the operating room early in the course of infarction, before severe myocardial necrosis has occurred. RV infarction is a relative contraindication to bypass surgery because it complicates the discontinuation of cardiopulmonary support.
12. **PCI in hospitals without surgical backup.** The C-PORT (Atlantic Cardiovascular Patient Outcomes Research Team) trial (61) found a reduced 6-month composite outcome of death, MI, and stroke in patients with acute MI randomized to primary PCI versus fibrinolytic therapy (12.4% vs. 19.9%; $p = 0.03$), even when PCI was performed in hospitals without surgical backup. All the community hospitals involved in this study underwent a formal “PCI development program.” Based on current PCI guidelines, it is reasonable to perform primary PCI at a facility that does not have surgical backup if there is a proven plan in place for rapid transfer to another hospital capable of performing cardiac surgery. This plan must involve the ability to use hemodynamic support if needed during transfer.

C. Adjuvant therapy

1. **β -Blockers.** Extensive data from the era before reperfusion established the usefulness of β -blockers in reducing recurrent ischemia, arrhythmias, and mortality. Several small randomized trials performed in the fibrinolytic reperfusion era confirmed the anti-ischemic and antiarrhythmic benefits, although short-term mortality was not affected. As a result, prior recommendations have stated that β -blockers should be administered to all patients within the first 24 hours of acute MI, unless contraindicated by severe reactive airway disease, hypotension, bradycardia, or cardiogenic shock. However, more recent data from the PCI era have shown no difference in mortality and no difference in the composite end point of death, reinfarction, or ventricular fibrillation arrest (62). The COMMIT/CCS-2 (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) trial, a large ($n = 22,929$) randomized controlled trial found that the metoprolol group had more ventricular fibrillation arrest (2.5% vs. 3.0%; $p = 0.001$) and shock (5.0% vs. 3.9%; $p < 0.001$). The incidence of shock was most notable in patients with Killip class II and III heart failure. This has led to a change in guidelines recommending more judicious use of early (< 24 hours) β -blockers, avoiding use in patients with significant signs of heart failure, low cardiac output, risk of cardiogenic shock, or other relative contraindications to their use (22).
- a. **For ongoing ischemia with tachycardia or hypertension,** after rapid evaluation of ventricular function, intravenous metoprolol can be given (5 mg every 5 minutes until the desired blood pressure and pulse are achieved). Patients who tolerate the intravenous loading can begin moderate oral doses (12.5 to 50 mg of metoprolol, two to four times daily). The dose should be subsequently titrated upward to the maximally tolerated dose (200 mg of sustained-release metoprolol, once daily). Use of β -blockers should be avoided in patients with tachycardia of unclear origin, as these

agents can decompensate heart failure in patients with compensatory tachycardia.

2. **Angiotensin-converting enzyme (ACE) inhibitors** can be started orally in the first 24 hours for all patients without hypotension, acute renal failure, or other contraindications. These medications were shown to reduce mortality in the GISSI 3 (62) and ISIS 4 (International Study of Infarct Survival) (63) trials. ACE inhibitors should be continued indefinitely in patients with LV dysfunction or clinical CHF, because these patients have been shown to derive a mortality benefit. In addition, the Heart Outcomes Prevention Evaluation (HOPE) study (64) found that high-risk patients, including those with prior MI but normal LV function, still had long-term benefit from ramipril. Intravenous formulations of these agents should not be used because they have not demonstrated benefit and may increase mortality. Rather, a graded oral regimen is advised. Angiotensin-receptor blockers remain a viable option for ACE inhibitor–intolerant patients.
3. **Calcium channel blockers.** Evidence for a potential increase in mortality has limited the use of calcium channel blockers in the care of patients with acute MI. They are indicated for the management of supraventricular tachyarrhythmia, cocaine-induced MI, or relief of postinfarction angina unresponsive to β -blockade. Otherwise, these agents should be avoided. Short-acting agents, such as nifedipine, are contraindicated because of their reflex sympathetic activation. Verapamil and diltiazem should be avoided in patients with LV dysfunction or CHF. Amlodipine is an effective antianginal agent and appears safe to use for this indication in patients with CHF.
4. **Magnesium.** There was once considerable enthusiasm for the routine use of intravenous magnesium in patients with MI, based on the findings of LIMIT 2 (Leicester Intravenous Magnesium Intervention Trial), which observed a 24% reduction in mortality compared with placebo. The larger ISIS 4 and MAGIC (Magnesium in Coronaries) trials failed to duplicate this benefit, however, and enthusiasm has waned. Some have speculated that the lack of effect in ISIS 4 was because of delayed administration or low control group mortality. In the modern era, magnesium is not routinely used other than to replete serum magnesium levels that are lower than 2.0 $\mu\text{g/dL}$ or for the management of *torsade de pointes* (1 to 2 g over 5 minutes).
5. **Aldosterone antagonists.** The use of aldosterone-blocking agents has been shown to be beneficial in post-MI patients. RALES (Randomized Aldactone Evaluation Study) found a reduction in all-cause mortality with the use of aldactone in patients with ischemic cardiomyopathy and NYHA class III or IV heart failure. However, the only randomized trial to address the use of such agents among patients with ventricular dysfunction after STEMI is EPHEUS (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), where eplerenone was found to reduce death, cardiovascular death, and hospitalization for heart failure.
6. **Diabetes control.** The DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) study found a significantly lower mortality rate at 1 year compared with standard therapy (8.6% vs. 18.0%; $p = 0.020$) in diabetic patients treated with aggressive blood glucose reduction with an insulin infusion during hospitalization, followed by multidose subcutaneous insulin injections. However, a small trial (OASIS-6 GIK) and a large (> 20,000 patients) randomized trial (CREATE-ELCA) failed to show any benefit to glucose–insulin–potassium (GIK) infusions. As a result, it appears prudent to institute sound glucose control, but it is not necessary to aggressively pursue glucose control with GIK infusions. Current guidelines suggest insulin therapy

to achieve and maintain blood glucose levels < 180 mg/dL while avoiding hypoglycemia (9).

7. **Antiarrhythmics.** The use of lidocaine or other antiarrhythmic agents is not warranted for the prophylactic suppression of ventricular tachycardia (VT) and fibrillation. Although lidocaine may decrease tachyarrhythmias, there is no survival benefit. There is also evidence to suggest an increase in mortality related to an increased incidence of bradycardia and asystole. In addition, there is evidence that “high-dose” amiodarone may actually increase mortality. Antiarrhythmic therapies are discussed in more detail in Chapter 21.
8. **Intraaortic balloon pump (IABP).** In the treatment of patients with cardiogenic shock, IABP counterpulsation is the preferred means of augmenting systolic pressure because use of an IABP decreases afterload and oxygen requirements while increasing diastolic coronary flow. IABP is contraindicated in the care of patients with marked aortic regurgitation, because it may worsen the regurgitation and cause rapid hemodynamic deterioration (see Chapter 63).
9. **Inotropic agents.** In general, these agents should be avoided whenever possible because of their tendency to increase myocardial oxygen demand and their associated risk of tachycardia and arrhythmias. If IABP counterpulsation proves insufficient, intravenous inotropic support may be warranted, but its use should be guided by means of pulmonary arterial catheter monitoring whenever possible.
 - a. **Patients with hypotension accompanied by a pulmonary capillary wedge pressure (PCWP) < 15 mm Hg** should be managed with rapid infusion of boluses of normal saline solution, as should patients with inferior MI who have concomitant RV infarction.
 - b. **After intravascular volume has been repleted** and the PCWP is > 15 mm Hg, dopamine may be indicated at doses up to $20 \mu\text{g/kg/min}$ if hypotension or signs of heart failure persist. Norepinephrine may be used as second-line therapy. The benefits of improved cerebral and systemic perfusion pressure by an increase in inotropy usually come at the cost of increased afterload and myocardial oxygen demand from vasoconstriction.
 - c. **Dobutamine** can be useful when PCWP is > 18 mm Hg in the setting of mild to moderate hypotension (70 to 90 mm Hg) or when nitroglycerin or nitroprusside is contraindicated because of the risk of inducing hypotension. Use of PDEs such as milrinone, which have combined vasodilating and inotropic actions, is problematic because of their arrhythmogenicity and their tendency to increase myocardial oxygen consumption. Use of these drugs to maintain adequate systemic pressure and forward output is acceptable if the other therapies have failed. The main goal, however, should be to avoid these agents or reduce the need for them in terms of absolute dose and duration.
10. **Implantable cardioverter-defibrillators (ICDs).** Posited to reduce the risk of sudden death following acute MI, ICDs were routinely implanted an average of 18 days following the index MI event in patients with reduced ventricular function and autonomic dysfunction (DINAMIT trial) (65). Although there was a decrease in cardiovascular death, this study failed to demonstrate any reduction in all-cause mortality. The Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) evaluated the benefit of delayed ICD insertion in patients with prior MI (66). The trial enrolled 1,232 patients with a history of MI at least 1 month prior to enrollment (90 days if bypass surgery was performed) and a left ventricular ejection fraction (LVEF) of $\leq 30\%$. Patients were randomized to prophylactic ICD insertion or standard medical therapy. At an average follow-up of 20 months, prophylactic insertion of an ICD significantly reduced all-cause

mortality (14.2% vs. 19.8% for standard therapy; HR 0.69; 95% CI, 0.51 to 0.93; $p = 0.016$) (66). According to current ACC/AHA guidelines, an ICD should be inserted in patients with ventricular fibrillation or hemodynamically significant sustained VT that occurs 48 hours after acute MI, assuming there is no recurrent ischemia or MI (67). Patients with an EF $\leq 35\%$ and NYHA class II or III heart failure secondary to an MI that occurred at least 40 days prior should also receive an ICD (67). In addition, patients who are 40 days post-MI with NYHA class I heart failure and an EF $\leq 30\%$ are candidates for ICD insertion (67). Lastly, any patient with a prior MI, nonsustained VT, EF $\leq 40\%$, and inducible ventricular fibrillation or sustained VT during an electrophysiological study should receive an ICD (67). Patients who have received CABG should have their LVEF and NYHA functional class reassessed 90 days after the procedure to determine ICD candidacy.

11. **Wearable cardioverter–defibrillators.** Patients who are considered at risk for SCD but do not meet the above criteria, such as patients waiting for reassessment of LVEF after CABG, can be given the option of a wearable cardiac defibrillator as a bridge to ICD implantation or recovery of LVEF. The efficacy of wearable cardioverter–defibrillators was evaluated by a two-component trial consisting of the WEARIT and BIROAD studies (68). The WEARIT study enrolled 177 patients with an LVEF $< 30\%$ and NYHA class III or IV heart failure. The BIROAD study enrolled 112 patients with a recent MI or CABG who were considered high risk for SCD but did not meet criteria for or refused ICD implantation. During the 901 patient-month observation period, there were six successful and two unsuccessful defibrillations (68). Both unsuccessful defibrillation attempts were due to the device being worn incorrectly (68). During the study, there were six instances of SCD. Five cases were secondary to the device not being worn and in one case the device was being worn incorrectly (68). While wearable cardioverter–defibrillators are currently not recognized in the ACC/AHA guidelines, there appears to be a benefit in select patients.
12. **Anticoagulation for large anterior wall MIs.** Historical teaching (not based on randomized data) has advocated anticoagulating patients for 6 weeks after a large anterior wall MI, with the goal of preventing LV thrombus development. However, in the era of primary PCI with coronary stenting, this recommendation would necessitate treatment with aspirin, clopidogrel, and coumadin, placing patients at fairly high risk for bleeding. Some clinicians recommend anticoagulation only if there is objective evidence of LV thrombus by echocardiography. Others still recommend empiric anticoagulation, but with a slightly lower target international normalized ratio (1.5 to 2.0).

X. ACUTE MI ASSOCIATED WITH COCAINE ABUSE. The pathophysiologic process and management of acute MI associated with cocaine use differ from those of classic MI.

A. Pathophysiology

1. **The underlying pathophysiologic factor** in acute MI associated with cocaine abuse is believed to be coronary spasm or thrombus formation caused by α -adrenergic stimulation. This can occur in a normal segment of artery or be superimposed on mild to moderate atherosclerosis. Atherosclerosis is accelerated by chronic cocaine use.
 2. **Increased oxygen demand** caused by β -adrenergic stimulation of heart rate and contractility also contributes to the onset of ischemia.
- B. Clinical presentation.** Chest pain caused by infarction after cocaine ingestion typically occurs within 3 hours, although it can vary from minutes to days, and depends on the route of administration (median of 30 minutes with intravenous cocaine,

90 minutes with crack smoking, and 135 minutes with nasal inhalation). More than 80% of persons with infarction are also cigarette smokers. Studies with animals have demonstrated a synergistic effect between cigarette smoking and cocaine use.

C. Therapy

1. The **initial management** of ST-segment elevation associated with cocaine use includes the routine administration of aspirin, oxygen, and heparin. Aggressive use of sublingual and intravenous nitroglycerin or intravenous calcium channel blockers is advised in an effort to relieve coronary spasm. Intravenous benzodiazepines should also be given, as they not only relieve cocaine induced chest pain but also improve cardiac hemodynamics (69).
2. **β -Blockers are contraindicated in patients with cocaine-induced acute MI.** Although they block undesirable β -adrenergic effects, these agents allow unopposed α -adrenergic stimulation and have been associated with increased mortality in nonrandomized analyses.
3. **Reperfusion therapy must be considered if vasodilator therapy is unsuccessful** in relieving symptoms and ST-segment changes.
4. **Immediate angiography and mechanical revascularization as appropriate** may be even more beneficial in cocaine-induced MI patients. Many patients who use cocaine have contraindications to thrombolysis, such as severe hypertension or persistent vasospasm without thrombosis, which is not amenable to thrombolytic therapy.

XI. POSTOPERATIVE ACUTE MI

- A. **Etiology and pathophysiology.** Acute MI following noncardiac operations most commonly occurs on the third or fourth postoperative day. Conventional theory was that MI was caused by a combination of increased oxygen demand and arterial shear stress associated with the increased adrenergic drive that accompanies pain and ambulation in the postoperative period. Intravascular volume shifts caused by redistribution of fluids, intravenous administration of fluids, and decreased enteral intake all contribute to the risk of postoperative MI. It is apparent that there is a postoperative inflammatory state associated with hypercoagulability, marked by an increase in fibrinogen and other acute-phase reactants. Recent data would indicate that perioperative management of patients with DESs may be problematic, as risk of stent thrombosis may be speculated to be increased in this milieu, whereas antiplatelet therapies are discontinued to reduce bleeding risks.
- B. **Therapy.** Management is complicated by limitations on the use of fibrinolytic agents and anticoagulant therapies. Therapy relies more heavily on the intravenous use of β -blockers and urgent angiography and mechanical reperfusion. The optimal antiplatelet or anticoagulation regimen for recent (< 1 year) DES patients undergoing noncardiac surgery is not known.

XII. SIMPLIFIED REPERFUSION STRATEGY. The wealth of data regarding reperfusion strategies and adjunctive therapies in acute MI detailed previously may lead to confusion regarding the optimal approach. Based on guideline recommendations, a simplification of the STEMI management strategy can be achieved.

- A. **For patients presenting with acute MI where primary PCI is available,** a reasonable strategy would involve prehospital administration of aspirin, parenteral anticoagulation, and a platelet P2Y₁₂ receptor inhibitor, as well as nitrates and β -blocker therapy if not contraindicated, and immediate transfer to the catheterization laboratory. The decision for GP IIb/IIIa therapy and whether coronary stenting should be performed with BMS or DES should be left at the discretion of the interventional cardiologist. If the patient does not have decompensated heart failure or renal failure, assessment of ventricular function should be performed, allowing risk stratification

and initiation of additional adjunctive therapies such as statins, ACE inhibitors, and aldosterone antagonists.

- B. For patients presenting to a hospital where primary PCI is not available, but immediate transfer (medical contact to balloon time < 120 minutes) to a PCI facility is available,** a similar strategy is employed, with initiation of aspirin, platelet P2Y₁₂ receptor antagonist, anticoagulation, nitrates, and β -blockers prior to transfer, although patients at high risk with potentially longer transfer times may benefit from the addition of GP IIb/IIIa inhibitor or half-dose fibrinolytics plus GP IIb/IIIa inhibitor prior to transfer.
- C. If anticipated transfer times will exceed the medical contact-to-PCI time of 120 minutes,** then fibrinolytic therapy should be instituted in eligible patients within 30 minutes of medical contact. The choice of UFH or enoxaparin remains operator dependent, with either option reasonable. Among patients receiving fibrinolytics, immediate transfer to a PCI facility is preferable, and early angiography (< 24 hours) is recommended. Full-dose fibrinolytics followed by immediate transfer for coronary angiography should be performed in any patient with cardiogenic shock, severe CHF, or ventricular arrhythmia causing hemodynamic compromise, provided that the patient is a suitable candidate for revascularization.

ACKNOWLEDGMENTS: *The author thanks Drs. Deepak P. Vivekananthan, Michael A. Lauer, and Ryan D. Christofferson for their contributions to earlier editions of this chapter.*

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Unstable Angina and Non–ST-Segment Elevation Myocardial Infarction

I. INTRODUCTION. Unstable angina (UA) and non–ST-segment elevation myocardial infarction (NSTEMI) remain leading causes of morbidity and mortality in the United States, accounting for more than 1.5 million hospital admissions in the year 2004 alone. These conditions are part of a continuum of acute coronary syndromes (ACSs) that range from UA and NSTEMI to ST-segment elevation myocardial infarction (STEMI). **The clinical presentation of non–ST-elevation acute coronary syndrome (NSTEMI) can be variable, ranging from progressive exertional angina to postinfarction angina.** Because NSTEMI is distinguished from UA by the presence of elevated serum levels of cardiac biomarkers, serial measurements in patients presenting with ACS should be performed. With improvements in the diagnosis and risk stratification of patients with UA and NSTEMI, therapeutic approaches to NSTEMI-ACS have continued to evolve.

II. CLINICAL PRESENTATION

A. Risk factors

1. **Clinical characteristics indicative of high risk.** Symptoms may include an acceleration of ischemic symptoms within the preceding 48 hours, angina at rest (> 20 minutes), congestive heart failure (S_3 gallop, pulmonary edema, and rales), known reduced left ventricular (LV) function, hypotension, new or worsening mitral regurgitation murmur, age > 75 years, diffuse ST-segment changes on an electrocardiogram (ECG, ≥ 0.5 to 1 mm), and the presence of elevated serum cardiac biomarkers (typically creatine kinase myocardial band [CK-MB], troponin T, or troponin I). Patients at intermediate or low risk have angina of short duration, have no ischemic ST-segment changes on ECG, are negative for cardiac biomarkers, and are hemodynamically stable (Table 2.1).
2. **Electrocardiogram.** The initial ECG can help risk-stratify patients with UA. Ideally, this should be performed within 10 minutes of arrival to the emergency department (ED). Patients with ST-segment deviation (i.e., ST-depression or transient ST-elevation) ≥ 0.5 mm or with pre-existing left bundle branch block (LBBB) are at increased risk for death or myocardial infarction (MI) at 1 year after presentation. ST-segment elevation ≥ 0.5 mm in lead aVR raises the possibility of left main or three-vessel coronary artery disease (CAD). **T-wave inversions alone are generally not predictive of adverse ischemic events.**
3. **NSTEMI.** NSTEMI predicts a poorer prognosis among patients with NSTEMI-ACS. Multivariate predictors of NSTEMI in patients with ACS include **prolonged chest pain** (> 60 minutes), **ST-segment deviations** (depression or transient elevation), and **new or recent onset of angina** (in the past month). Elevations in the levels of troponin I or troponin T, contractile proteins released

TABLE 2.1 Risk Stratification of Patients with Unstable Angina

High risk ^a	Intermediate risk	Low risk
One of the following must be present:	No high-risk feature but must have one of the following:	No high- or intermediate-risk features present
Accelerating tempo of ischemic symptoms in preceding 48 h	Prior MI, peripheral or cerebrovascular disease	
Prolonged ongoing rest pain (> 20 min): moderate or high likelihood of CAD	Prolonged rest pain (> 20 min) that resolves	Increased frequency or duration of angina
Pulmonary edema: most likely caused by ischemia	Rest angina (> 20 min or relieved with rest or sublingual NTG)	Angina provoked by less exertion
Rest angina with dynamic ST changes ≥ 0.5 mm	Nocturnal angina	New-onset angina (within 2 wk to 2 mo)
New or worsening rales, S ₃ , or MR murmur	New-onset, severe angina within 2 wk with moderate or high likelihood of CAD	
Hypotension, bradycardia, tachycardia		
Bundle branch block, new or presumed new	T-wave changes	Normal or unchanged ECG
Sustained ventricular tachycardia	Pathologic Q waves or resting ST depression (< 1 mm) in multiple lead groups	
Positive serum cardiac biomarkers	Slightly elevated CK-MB, troponin T, troponin I (e.g., troponin T 0.01 ng/mL but < 0.1 ng/mL)	Normal cardiac markers
	Age older than 70 y	

CAD, coronary artery disease; CK-MB, creatine kinase myocardial band; ECG, electrocardiogram; MI, myocardial infarction; MR, mitral regurgitation; NTG, nitroglycerin.

^aRisk stratification involves considering clinical characteristics and ECG findings to make early triage decisions.

from necrotic cardiac myocytes, are independently predictive of morbidity and mortality among patients with UA (discussed later). According to the European Society of Cardiology/American College of Cardiology (ESC/ACC), troponin elevations in this clinical setting are, by definition, NSTEMI.

4. **Clinical risk classification systems.** Numerous scores have been derived to facilitate risk assessment and guide medical therapy in patients with NSTEMI-ACS. It is important to note that these scores can also be used to determine which patients may benefit most from early invasive therapy as opposed to a more conservative approach. The **Braunwald classification system** risk-stratifies patients with UA at presentation (Table 2.2). Braunwald defined UA according to the **characteristics of anginal pain** and the **underlying cause**. Patients with

TABLE 2.2 Braunwald Classification of Unstable Angina

Class	Characteristics ^a
I	Exertional angina New onset, severe, or accelerated Angina of < 2 mo duration More frequent angina Angina precipitated by less exertion No rest angina in the last 2 mo
II	Rest angina, subacute Rest angina within the last month but none within 48 h of presentation
III	Rest angina, acute Rest angina within 48 h of presentation
Clinical circumstances	
A	Secondary unstable angina Caused by a noncardiac condition, such as anemia, infection, thyrotoxicosis, or hypoxemia
B	Primary unstable angina
C	Postinfarction unstable angina Within 2 wk of documented myocardial infarction

^aThis classification can be used for risk stratification. Clinical characteristics at presentation and severity of angina are considered.

increasing Braunwald class have been shown to have increasing risk of recurrent ischemia and death at 6 months. Vital clinical characteristics not included in this classification were age, the presence of comorbid conditions (e.g., diabetes mellitus and renal insufficiency), electrocardiographic criteria, and the presence of positive cardiac markers.

The thrombolysis in myocardial infarction (TIMI) UA risk score, based on the TIMI IIB and ESSENCE trials, incorporates **the combination of age, clinical characteristics, ECG changes, and cardiac markers for risk stratification** (Table 2.3). A higher risk score correlated with an increase in the incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization. The GRACE prediction score, which incorporates nine clinical variables derived from the medical history and clinical findings on initial presentation and during hospitalization, can be used to estimate the in-hospital and 6-month outcomes for patients hospitalized with any form of ACS. Other risk stratification scores based on the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial and the GUSTO IV–ACS trial (Table 2.4) have also been described. Together, these various clinical risk stratification systems help identify high-risk patients likely to benefit most from more aggressive therapy.

TABLE 2.3 Thrombolysis in Myocardial Infarction Risk Score

Score	Incidence of death, new or recurrent MI, and recurrent ischemia requiring revascularization (%)
0/1	4.7
2	8.3
3	13.2
4	19.9
5	26.2
6/7	40.9

Scoring system	
One point when risk factor is present, zero points if absent (a total of seven points are possible): Age > 65 y	
Presence of more than three risk factors for coronary artery disease	
Prior coronary stenosis $\geq 50\%$	
Presence of ST-segment deviation on admission electrocardiogram	
More than two episodes of angina within the past 24 h	
Prior use of aspirin in past 7 d	
Elevated cardiac markers	

- B. Demographics.** Compared with STEMI, patients with **UA/NSTEMI** tend to be **older** and have a higher incidence of **cardiac risk factors or comorbid conditions** (e.g., **diabetes, hypertension, and hypercholesterolemia**) and a greater likelihood of **prior MI and revascularization procedures** (i.e., percutaneous coronary intervention [PCI] and coronary artery bypass grafting [CABG]).
- C. Signs and symptoms.** Chest pain due to UA may be rest pain or may be triggered with minimal exertion and can be new onset or increased in severity and frequency or precipitated with less effort than prior angina. Compared with stable angina, **chest pain in UA** is usually more **severe and protracted**, often requiring several doses of sublingual nitroglycerin or extended periods of rest for relief. UA or NSTEMI cannot be differentiated on the basis of chest pain characteristics or ECG abnormalities alone. **The only way this determination can be made is with evidence of myocardial necrosis by measurement of cardiac biomarkers.**
- D. Differential diagnosis.** It is vitally important to determine the probability that the chest pain or presenting symptom(s) are caused by ACS resulting from obstructive CAD. The exclusion of other diagnoses that mimic angina such as costochondritis, pneumonia, or pericarditis, as well as other life-threatening conditions such as aortic dissection, pneumothorax, and pulmonary embolus, is essential. Hypertensive urgency or emergency, thyrotoxicosis, systemic infection, anemia due to blood loss, and other precipitating causes of myocardial ischemia and secondary UA should also be sought.

TABLE 2.4 **GUSTO Risk Score**

Risk score	30-Day mortality rate (%)
0–5	0.4
6–10	2.8
11–15	8.7
16–19	25.0
20–22	41.7

Scoring system	
Points are assigned based on the following criteria:	
Age (y)	Points
50–59	2
60–69	4
70–79	6
80+	8
Clinical history	
Prior heart failure	2
Prior stroke/TIA	2
Prior MI/revasc./chronic angina	1
Vitals and laboratory values	
Heart rate ≥ 90 beats/min	3
Elevated troponin and CK-MB	3
Creatinine > 1.4 mg/dL	2
CRP (μg/L) > 20	2
10–20	1
Anemia	1

CK-MB, creatine kinase myocardial band; CRP, C-reactive protein; GUSTO, Global Utilization of Strategies to Open Occluded Arteries; MI, myocardial infarction; revasc., revascularization; TIA, transient ischemic attack.

E. Physical findings. Physical examination alone is insufficient for the diagnosis of UA. **Signs of heart failure** (elevated jugular venous pressure, S_3), impaired myocardial performance (S_4), or peripheral vascular disease (i.e., bruits over major vessels) may be present. These findings predict a higher likelihood of significant CAD.

III. PATHOPHYSIOLOGY. The pathophysiology of ACS encompasses a complex interplay of plaque erosion or rupture, platelet activation and aggregation leading to thrombus formation, endothelial dysfunction, vasospasm, and vascular remodeling.

A. Plaque rupture. UA, NSTEMI, and STEMI share a common initiating event: atheromatous plaque fissure or rupture. Plaque rupture exposes thrombogenic components stimulating platelet deposition, activation, and aggregation at the site

of injury, followed by activation of the coagulation cascade and thrombus formation. Factors contributing to plaque instability include lymphocyte and macrophage activation and increased inflammation. Ruptured plaques or culprit lesions in patients, even when medically stabilized, tend to progress in comparison with stable lesions. Follow-up angiography of 85 patients with UA who were medically stabilized 8 months after initial presentation revealed that 25% of culprit lesions progressed in disease severity (usually to complete occlusion), compared with 7% of nonculprit lesions. This progression of disease correlated with future cardiac events.

- B. Thrombus formation.** Exposure of circulating platelets to subendothelial contents results in platelet adhesion, aggregation, and, ultimately, thrombus formation. With platelet activation, the glycoprotein (GP) IIb/IIIa receptor on the platelet surface undergoes a conformational change, facilitating further platelet activation and aggregation. This markedly increases thrombin production, further expanding and stabilizing the thrombus.
- C. Vasospasm** can be induced by the local production of vasoactive substances released from the subendothelial matrix or propagating thrombus or it can occur as a primary phenomenon. Severe localized spasm of a coronary artery segment (i.e., Prinzmetal's angina) may also result in ACS. This vasospasm frequently occurs at sites of unstable plaque and is thought to contribute to thrombus formation. Even angiographically normal coronary arteries with underlying endothelial dysfunction may be subject to vasospasm.
- D. Multiple lesions.** Although a single culprit lesion is often found at angiography, multiple culprit lesions are not uncommon in patients presenting with UA/NSTEMI, attesting to the global nature of the disease. In a substudy of patients with NSTEMI, **multiple apparent culprit lesions were found in 14% of patients**, whereas a single culprit lesion was found in 49%. An intravascular ultrasound study of patients with NSTEMI undergoing angiography and possible PCI revealed an average of 2.1 plaque ruptures per patient, with 79% of patients having a lesion in a location different from that of the culprit lesion.
- E. Secondary causes.** UA can also result from a supply–demand mismatch of oxygen delivery to the myocardium. With stable obstructive coronary lesions, precipitants of UA include **increased myocardial oxygen demand** (i.e., tachycardia, severe hypertension, cocaine use, hyperthyroidism, fever, or sepsis) and **decreased oxygen supply** (i.e., anemia or hypoxemia).

IV. INITIAL EVALUATION AND MANAGEMENT

A. Initial triage and clinical assessment recommendations

1. Patients with symptoms suggestive of ACS should be instructed to call 911 immediately. It is recommended that the patient be transported to the hospital by ambulance rather than by friends or relatives.
2. Prehospital emergency service providers should give 162 to 325 mg of aspirin to patients who have symptoms suggestive of ACS, unless it is contraindicated. The patient should be instructed to chew the aspirin rather than swallow it whole so as to facilitate rapid absorption.
3. Patients who have been prescribed nitroglycerin should be instructed to take only one dose in response to chest pain. If the symptoms have not improved or are worsening within 5 minutes, then the patient should call 911 immediately before taking additional nitroglycerin. If the patient is known to have chronic stable angina and the chest pain is significantly improving after taking a dose of nitroglycerin, it is appropriate to instruct the patient to take additional doses of nitroglycerin every 5 minutes for a total of three doses and then call 911 if symptoms have not completely resolved.

4. Patients with suspected ACS who have had anginal symptoms at rest for greater than 20 minutes, hemodynamic instability, or recent syncope should be referred immediately to the ED.

B. Early risk stratification recommendations

1. Patients who present with suspected ACS should be quickly assessed and should undergo early risk stratification for adverse cardiovascular events. This should include a history and physical examination focused on high-risk features of ACS (prolonged chest pain at rest, syncope, signs of CHF, etc.), an ECG, and laboratory biomarkers of cardiac injury, preferably troponin I or T.
2. **A 12-lead ECG should be performed immediately upon arrival at the ED, with the standard being within 10 minutes of arrival for patients with symptoms suggestive of ACS.**

Common ECG findings in UA/NSTEMI include ST-segment depression, transient ST-segment elevation, and T-wave inversion. However, approximately 20% of patients with an NSTEMI confirmed by cardiac enzymes have no ischemic ECG changes. Moreover, a “normal” ECG pattern is not sufficient to rule out ACS in patients with chest pain (> 4% of patients presenting with chest pain and normal ECG patterns are diagnosed with UA). Persistent ST-segment elevation of ≥ 1 mm in two or more contiguous leads or new LBBB suggests acute STEMI and should be considered for emergency reperfusion therapy (see Chapter 1). As previously mentioned, ST-segment elevation ≥ 0.5 mm in lead aVR raises the possibility of left main or three-vessel CAD. T-wave inversions are the least specific of ECG changes in ACS. However, new, deep, symmetric T-wave inversions of ≥ 2 mm across the precordium in patients presenting with UA (Wellens’ syndrome) often correspond to acute ischemia, usually related to a severe proximal left anterior descending artery stenosis. In this setting, revascularization often results in improved ventricular function and normalization of the ECG.

- a. Older classification systems recognized NSTEMI as non-Q-wave MI because myocardial necrosis occurs without ECG evidence of transmural injury. Because of the inability to determine the transmural extent of myocardial injury based on the presence or absence of ST-segment elevation, NSTEMI has become the preferred terminology.
- b. Analysis of 1,473 UA or NSTEMI patients in the **TIMI III trial** revealed transient ST-segment elevation in 10%, ST-segment depression in 33%, T-wave inversion in 46%, and no ischemic ECG changes in 9%.
3. **In patients in whom the initial ECG is not diagnostic** but the anginal symptoms persist, serial ECGs should be performed in 15- to 30-minute intervals. This is done in order to detect the development of ST-segment depression or elevation. Posterior circulation ischemia/infarction should be suspected and the use of posterior ECG leads and echo imaging should be considered.
4. Cardiac biomarkers should be measured in all patients presenting with symptoms suggestive of ACS. The preferred and recommended biomarker is a cardiac-specific troponin (troponin I or T). Patients with negative cardiac biomarkers within 6 hours of symptom onset should have the biomarkers remeasured at 8 to 12 hours after the onset of symptoms.
 - a. **Troponins.** Cardiac troponin I and T are contractile proteins found only in cardiac myocytes and are the preferred assays to document the presence of cardiac necrosis. Many clinical trials have used troponin levels for diagnosis and prognosis in ACS. Serum levels of troponins I and T typically rise within 3 to 12 hours after myocardial necrosis and remain elevated afterward for much longer than creatine kinase (CK; 10 to 14 days). Although troponins are more sensitive and specific for myocardial injury than CK and CK-MB, elevated troponin levels can be seen in other nonischemic cardiac conditions

(advanced heart failure and acute pericarditis) and in the setting of renal insufficiency. In the setting of NSTEMI-ACS, troponins have important prognostic significance beyond that specified by clinical criteria, with elevated levels portending a worse prognosis. In the **GUSTO IIb** trial of patients with UA, the 30-day mortality rate for patients with an elevated troponin T level (> 0.1 ng/mL) was 11.8%, compared with 3.9% for patients with normal troponin levels. Elevated troponin levels in the setting of NSTEMI-ACS have also been associated with increased likelihood of multivessel disease, high-risk culprit lesions, and intracoronary thrombus visible at the time of angiography.

- b. **Creatine kinase.** Among the most commonly used biochemical markers for the evaluation of patients with suspected ACS are CK and the MB isoenzyme of CK, measured serially every 6 to 8 hours for the first 24 hours. Total CK levels **peak at 12 to 24 hours** after the onset of symptoms, and **CK-MB levels peak at 10 to 18 hours** after the onset of symptoms. The CK-MB isoenzyme is more specific and more sensitive than the total CK measurement for documenting myocardial necrosis. Although a low level of CK and CK-MB is usually found in normal patients, values above the upper limit of normal for a given laboratory suggest the presence of myocardial necrosis. **Many nonischemic conditions, such as pericarditis, skeletal muscle injury, and renal failure,** can cause elevations of total CK levels or, less likely, an increase in CK-MB.
 5. The initial evaluation should include consideration and appropriate evaluation of noncoronary causes of the unexplained symptoms (see Section II.D).
- C. **Recommendations for immediate management and triage.** The initial management of patients with suspected ACS is dependent on the predicted risk of adverse cardiovascular outcomes. Patients can be initially categorized as low, intermediate, or high risk depending on the historical and clinical findings (Table 2.1). The use of risk stratification models such as the TIMI (Table 2.3), GRACE, and PURSUIT risk scores can also assist in determining which patients are at increased risk.

Patients with probable or possible ACS whose initial 12-lead ECG and cardiac biomarker levels are normal should be monitored on telemetry. Repeat ECGs and repeat cardiac biomarker measurements should be performed at scheduled intervals 6 to 8 hours apart.

1. In **low- and intermediate-risk patients** (Table 2.1) whose serial ECGs and cardiac biomarkers are normal, a conservative strategy may be considered and a **cardiac stress test** should be performed in the ED or monitoring facility. For low-risk patients, it is also appropriate to consider performing the stress test as an outpatient within 72 hours. The optimal time for testing may be determined at the discretion of the physician and in consideration of the patient's wishes. For such patients who are referred for outpatient stress testing, the initiation of antiplatelet and anti-ischemic pharmacotherapy (nitroglycerin and β -blockers) should be strongly considered.
2. **High-risk patients** (Table 2.1) and low-risk patients who have a positive stress test with high-risk features should be admitted to the hospital for inpatient management. Patients with active ongoing ischemia or hemodynamic or electrical instability should be admitted to the intensive care unit.
3. **Noninvasive stress testing.** Stress testing has been thought to be contraindicated in the evaluation of patients with UA because of the concern for acute occlusion with increased cardiac workloads in the presence of unstable plaques. However, patients at low or even intermediate risk who remain pain free for at least 12 to 24 hours and without any symptoms of heart failure can safely undergo functional testing. Intermediate-risk patients include those with age > 70 years; slightly elevated cardiac biomarkers (e.g., troponin T > 0.01 ng/mL but

< 0.1 ng/mL); T-wave changes; pathologic QS; minimal resting ST-depression (< 1 mm) on ECG; rest angina or present with atypical symptoms; and prior history of MI, CABG, peripheral or cerebrovascular disease, or aspirin use.

- a. Patients who have **normal myocardial perfusion scan** without fixed or reversible perfusion defects can be safely **discharged** from the hospital and followed up on an outpatient basis. However, **cardiac catheterization** should be considered for patients found to have high-risk features on stress testing because they are at increased risk for adverse ischemic events.
- b. If patients are unable to exercise, **pharmacologic stress testing** can be performed instead with dobutamine or a vasodilator such as adenosine or regadenoson. However, no large-scale studies using these modalities for stress testing have been performed in this patient population.

V. EARLY HOSPITAL CARE. The mainstay of treatment for ACS is directed at anti-ischemic therapy and antithrombotic (antiplatelet and anticoagulation) therapy. In clinical practice, the choice of specific antithrombotic therapy is partly determined by whether an initial conservative or an initial invasive approach is planned.

A. Anti-ischemic therapy. All patients admitted to the hospital with ACS should have their activity limited to bed or chair rest to help maintain minimal myocardial demand. Continuous ECG monitoring (telemetry) is recommended, and supplemental oxygen should be provided for patients who are in respiratory distress or have an oxygen saturation < 90%. The following anti-ischemic medications should also be considered.

1. **Nitrates.** Despite a lack of randomized clinical trial data, nitrates remain the mainstay of treatment for patients with UA with chest pain or spontaneous ischemia.
 - a. **Dosing.** Sublingual nitroglycerin or nitroglycerin spray (0.4 mg) should be administered immediately and repeated every 5 minutes (three times) to relieve anginal discomfort. If angina persists, intravenous nitroglycerin may be started (at 10 to 20 μ g/min). Intravenous nitroglycerin can be quickly titrated (5 to 10 μ g/min increases every 5 to 10 minutes) to relieve angina. Caution must be exercised as it may cause profound hypotension. Topical (nitroglycerin transdermal patch, 0.2 to 0.6 mg/h, or nitropaste, 1 to 2", replaced every 6 hours) or oral (isosorbide dinitrate, 10 to 40 mg orally three times daily, or isosorbide mononitrate, 30 to 120 mg orally each day) nitrates can also be used in patients to prevent recurrent anginal symptoms. Tolerance to nitrates is dose and interval dependent and can occur within 24 hours of initiation, requiring higher doses of nitrates. After symptoms are controlled, changing from intravenous to topical or oral formulations with nitrate-free intervals can limit this phenomenon.
 - b. **Contraindications.** Contraindications are known **hypersensitivity to nitrates and hypotension**. **Sildenafil (Viagra) use** within the prior 24 hours has been associated with hypotension, MI, and death.
2. **β -Blockers.** β -Blockers may relieve myocardial ischemia by lowering myocardial oxygen demand through its effects on blood pressure, heart rate, and contractility. A meta-analysis of 4,700 patients with UA and impending MI showed that β -blockers reduced the risk of MI, but no clear effect on mortality was seen. The goals of therapy are a resting heart rate of usually 50 to 60 beats/min and relief of angina. Cardioselective β -blockers (e.g., metoprolol and atenolol) are typically used to minimize side effects.
 - a. **Dosing.** Patients with ongoing anginal pain or persistent hypertension can initially be treated with intravenous β -blockers. Intravenous metoprolol can be given in 5-mg increments every 5 to 10 minutes until the desired heart rate and blood pressure response is achieved. Oral metoprolol therapy can

then be started at a dose of 25 to 50 mg every 6 to 12 hours and can be subsequently titrated as necessary.

- b. Contraindications.** Contraindications to β -blocker therapy include **advanced atrioventricular block, active bronchospasm, cardiogenic shock, hypotension, baseline bradycardia, and congestive heart failure.**
 - 3. Calcium channel blockers.** Calcium channel blockers have diverse physiologic effects, including vasodilation, decreased or slowed atrioventricular conduction, and negative inotropy and chronotropy. A meta-analysis of calcium channel blocker trials in the management of UA showed no effect on death or nonfatal MI. However, short-acting nifedipine increased the risk of MI or recurrent angina compared with metoprolol. Diltiazem may reduce adverse events among patients with UA with normal LV function. However, patients with LV dysfunction or pulmonary congestion on physical examination are reported to have worse outcomes when treated with diltiazem.
 - a. Indications.** Calcium channel blockers are recommended for patients with UA, but **only in patients with contraindications to β -blockers or when β -blockers and nitrates fail to fully relieve symptoms of ischemia.** Calcium channel blockers are preferred in patients with variant angina or cocaine-induced vasospasm.
 - b. Contraindications.** Contraindications to calcium channel blockers include LV dysfunction or signs and symptoms of congestive heart failure, hypotension, or atrioventricular conduction abnormalities.
 - 4. Angiotensin-converting enzyme (ACE) inhibitors.** In patients with LV dysfunction, ACE inhibitors improve survival and ventricular remodeling. The effects of ACE inhibitors in the care of patients with UA or NSTEMI are less well defined. However, **if patients have LV dysfunction, ACE inhibitors should be added to existing medical therapy.** Moreover, in the long term, ACE inhibitors should be considered in every patient with UA/NSTEMI, especially given the overall favorable data for their use in patients with CAD.
 - B. Initial conservative versus initial invasive strategy.** Two approaches to managing patients with NSTEMI-ACS have evolved. Based on a host of factors, including an overall assessment of patient risk, a decision to pursue either an early invasive strategy or an initial conservative strategy needs to be made early in the management of NSTEMI-ACS (Table 2.5). Overall, patients selected to have early invasive therapy will have coronary angiography performed within 24 hours of admission, or sooner, depending on the clinical situation. Those patients elected to a conservative strategy are managed with optimal medical therapy and undergo angiography only in select circumstances such as development of recurrent symptoms or objective evidence of ischemia while on appropriate medical therapy. There have been several studies comparing these two strategies. Bavry et al. performed a contemporary meta-analysis of seven randomized trials evaluating an early invasive versus a conservative approach in the management of patients with NSTEMI-ACS. In this pooled analysis of 8,375 patients, there was a 25% relative reduction in all-cause mortality at 2 years with use of early invasive as compared with conservative therapy (4.9% vs. 6.5%, $p = 0.001$). Early invasive therapy also reduced the incidence of nonfatal MI and rehospitalization for UA by 17% and 31%, respectively.
 - 1.** The 2011 UA/NSTEMI ACC/AHA guidelines provide specific treatment strategies for the following patient populations:
 - a.** Patients who have **refractory angina despite medical therapy, hemodynamic instability, or electrical instability** are recommended to undergo an **early invasive strategy.**
 - b.** For patients who are **initially stabilized but are at high risk for adverse events**, it is reasonable to undergo an **early invasive strategy or an initially**

TABLE 2.5 Initial Management Strategy in NSTEMI-ACS: Early Invasive versus Conservative (Selective Invasive) Approach

Early invasive	Conservative
Hemodynamic instability	Low risk score (e.g., TIMI, GRACE, and PURSUIT)
Arrhythmia instability	Physician or patient preference in low- to intermediate-risk patient
High risk score (e.g., TIMI, GRACE, and PURSUIT)	
Elevated troponin T or I	
Refractory angina despite aggressive medical therapy	
Prior PCI within 6 mo or prior CABG	
Signs or symptoms of congestive heart failure	
New or worsening mitral regurgitation	
Left ventricular function < 40%	

CABG, coronary artery bypass grafting; GRACE, Global Registry of Acute Coronary Events; NSTEMI-ACS, non-ST-elevation acute coronary syndrome; PCI, percutaneous coronary intervention; PURSUIT, Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; TIMI, thrombolysis in myocardial infarction.

conservative strategy. This includes patients who are troponin positive. The decision of which strategy to employ should be based upon both physician and patient preference.

- c. For patients who are **not at high risk**, it is reasonable to proceed with a **delayed invasive approach**.
 - d. **Women with low-risk features** are recommended to proceed with a **conservative strategy**.
 - e. For patients with **extensive comorbid conditions** (e.g., cancer and liver or pulmonary failure), **an early invasive strategy is not recommended**. This is particularly true when the risks of revascularization are likely to outweigh the benefits.
 - f. It is **not recommended to proceed with an early invasive strategy** in patients with **acute chest pain and a low likelihood of ACS**.
 - g. Patients who are **not willing to undergo coronary revascularization** **should not undergo an early invasive strategy**.
2. **Randomized trials.** The following is a summary of the randomized trials that have compared an early invasive versus an early conservative approach in different patient populations.
 - a. Two earlier trials performed prior to the current era of antiplatelet therapy and coronary stenting were the **TIMI IIIB** and **VANQWISH** trials. Both of these trials showed similar long-term outcomes (death or MI) between early invasive and conservative treatment strategies; however, there was an increase in early mortality associated with invasive therapy in the VANQWISH study,

and these two trials were excluded from the recent meta-analysis, since both are noncontemporary.

- b. In the **FRISC II** trial, patients with UA/NSTEMI were randomized in a factorial design to an early invasive or conservative strategy and to dalteparin or placebo. An early invasive strategy was associated with a reduction in the rate of death or MI at 6 months (9.4% vs. 12.1%, $p = 0.031$) and reduced symptoms of angina and rehospitalization, regardless of treatment with dalteparin.
- c. In the **TACTICS-TIMI 18** trial, patients with UA/NSTEMI treated with aspirin, heparin, and tirofiban were randomized to an early invasive or a conservative strategy. Patients assigned to an **early invasive approach underwent catheterization within 4 to 48 hours**, with revascularization as appropriate. Patients assigned to the conservative arm underwent cardiac catheterization only if there was objective evidence of recurrent ischemia or abnormal stress test. An early invasive strategy was associated with a reduction in the composite of death, nonfatal MI, or rehospitalization for ACS at 6 months (15.9% vs. 19.4%, $p = 0.025$), as well as a reduction in the incidence of death or nonfatal MI at 6 months (7.3% vs. 9.5%, $p < 0.05$).
- d. In the **RITA 3** trial, an early invasive strategy for moderate-risk patients with UA/NSTEMI was associated with a decreased rate of death, MI, or refractory angina compared with conservative therapy at 4 months (9.6% vs. 14.5%, $p = 0.001$). This was caused primarily by a reduction in refractory angina. These results suggest that even in moderate-risk patients, an early invasive strategy may be preferred. The RITA 3 investigators also reported a meta-analysis of trials comparing an early invasive versus a conservative approach, with an association between the early invasive approach and a decreased incidence of death or nonfatal MI at 1 year (relative risk [RR] = 0.88, 95% confidence interval [CI]: 0.78 to 0.99).
- e. In the **ISAR-COOL** trial, patients with UA/NSTEMI treated with intensive medical therapy (aspirin, heparin, clopidogrel [600-mg loading dose], and tirofiban) were randomized to immediate invasive therapy (median time of 2.4 hours) versus delayed invasive therapy after a “cooling off” period (median time of 86 hours). Those who had early intervention had a significant reduction in death or MI at 30 days compared with those who had a “cooling off” period (5.9% vs. 11.6%, $p = 0.04$).
- f. In the **ICTUS** trial, 1,200 patients with NSTEMI-ACS with elevated troponins were randomized to either early invasive therapy (angiography within 24 to 48 hours) or initial conservative strategy with selective invasive therapy. There was no difference in the primary composite end point of death, MI, or rehospitalization for ACS at 1 year between the two groups (22.7% vs. 21.2%, $p = 0.33$). The aggressive medical therapies and high rates of revascularization (47%) in the initial conservative strategy group are two among many potential explanations for the findings of this trial.
- g. In the **TIMACS** trial, patients with NSTEMI presenting within 24 hours of onset of symptoms were randomized to undergo angiography as soon as possible (within 24 hours) or after a minimum delay of 36 hours. These patients received contemporary medical therapy including acetylsalicylic acid (ASA), clopidogrel (>80%), heparin or fondaparinux, and GP IIb/IIIa inhibitors (23%). Overall, there was a nonsignificant trend toward a reduction in death, new MI, or stroke at 6 months for patients who received an early invasive strategy (11.3% for delayed angiography vs. 9.6% in the early intervention, $p = 0.15$). However, there was a significant reduction in the secondary end point of death, MI, or refractory ischemia for patients randomized to an early invasive strategy (12.9% vs. 9.5%, $p = 0.003$) that was primarily driven

by a decrease in refractory ischemia. Interestingly, patients who were in the highest tertile of risk according to the GRACE score were the most likely to benefit from an early invasive strategy. Overall, this study supports an early invasive strategy for patients presenting with UA/NSTEMI, particularly for those among the highest tertile of risk according to the GRACE scale.

- h. The **ABOARD** trial assessed whether a very aggressive strategy of emergent intervention (analogous to primary PCI for STEMI) would benefit patients presenting with UA/NSTEMI versus delayed angiography and intervention. Immediate angiography and intervention did not decrease the rate of the primary outcome of median troponin I release (2.1 ng/mL for the invasive strategy vs. 1.7 ng/mL for the delayed strategy) nor did it show a trend toward improved outcomes in the secondary end point of death, MI, or urgent revascularization at 1 month (13.7% for early invasive management vs. 10.2% for the conservative approach, $p = 0.31$).
- C. Antiplatelet and anticoagulant therapies.** There are many different antiplatelet and antithrombotic agents currently available for the treatment of ACS. As such, the decision of which combination of medications to use and when to administer them can be challenging. In general, the decision of which agents to use depends on (1) whether an early invasive strategy is used and (2) what post-angiography management strategy is employed. Regardless of which strategy is chosen, all patients presenting with ACS should receive a loading dose of aspirin (162 to 325 mg) to be chewed and swallowed; if the patient is aspirin intolerant, then a loading dose of clopidogrel (300 to 600 mg) should be given. The antiplatelet and anticoagulant therapies available for each of the following strategies are listed below. The specific doses, adverse effects, and pharmacokinetics of these agents are then listed separately.
1. **Initial conservative strategy.** After receiving aspirin, patients who undergo an initial conservative strategy should receive an **anticoagulant** and be started on **clopidogrel** therapy. Enoxaparin and fondaparinux are the anticoagulants of choice; unfractionated heparin (UFH) is an acceptable alternative. Of note, if fondaparinux is used and an invasive strategy is ultimately employed, then another anticoagulant with factor IIa activity (UFH) must be coadministered to prevent catheterization-associated thrombosis.
 2. **Initial invasive strategy.** After receiving aspirin, patients who undergo an initial invasive strategy should receive **anticoagulation with enoxaparin, UFH, or bivalirudin**. Before proceeding with catheterization, it is recommended to administer a **second antiplatelet agent**. These agents include clopidogrel or ticagrelor. Prasugrel may also be utilized after angiographic definition. A GP IIb/IIIa inhibitor such as eptifibatide or tirofiban may be considered.
 3. **Once angiography is performed, the appropriate subsequent therapy depends on the management plan.**
 - a. For patients undergoing **CABG surgery**, it is recommended to **continue aspirin therapy**. If clopidogrel therapy has been started, it should be discontinued 5 days prior to CABG. GP IIb/IIIa inhibitors should be discontinued 4 hours prior to CABG. Although ticagrelor is a reversible P2Y₁₂ inhibitor, bleeding rates were similar to clopidogrel following CABG when discontinued 5 days prior to surgery. Bleeding rates following CABG were greater with prior exposure to prasugrel compared with clopidogrel in the TRITON-TIMI 38 trial and the risk persisted for up to 7 days from last drug exposure. UFH can be continued until CABG; however, enoxaparin should be discontinued 12 to 24 hours prior to CABG and bivalirudin should be discontinued 3 hours prior to CABG.
 - b. **Percutaneous coronary intervention.** All patients undergoing PCI should be on dual antiplatelet therapy. Routine GP IIb/IIIa inhibitor prior to PCI is not warranted and may be used adjunctive to PCI in selective cases.

- c. **Medical therapy.** If the catheterization reveals no significant obstructive CAD, then the antiplatelet and anticoagulant therapy is to be continued at the discretion of the physician. If catheterization reveals significant CAD that is to be medically managed, then it is recommended to continue aspirin therapy and to load with clopidogrel therapy if not done so prior to catheterization. GP IIb/IIIa therapy should be discontinued. UFH should be continued for 48 hours; enoxaparin or fondaparinux should be continued for the duration of the hospitalization. Bivalirudin should be continued for 72 hours.
- 4. **Aspirin.** Despite being a relatively weak inhibitor of platelet aggregation, aspirin has a significant effect on mortality in UA. There are several pathways that lead to platelet activation, of which aspirin blocks only the cyclooxygenase-derived thromboxane A_2 pathway. Aspirin therapy for UA/NSTEMI has been studied in five major clinical trials at doses ranging from 75 to 325 mg/d. Overall, treatment with aspirin reduced the combined end point of death or nonfatal MI by 50%.
 - a. **Pharmacokinetics.** The onset of aspirin's antiplatelet effect is quite rapid, with substantial inhibition of thromboxane A_2 production within 15 minutes, translating into measurable platelet inhibition within 60 minutes. It should be given as soon as patients present with ACS. Because aspirin's inhibition of cyclooxygenase is irreversible, its antiplatelet effect is durable, lasting 7 to 10 days.
 - b. **Dosing.** Unless contraindicated (e.g., active bleeding and documented hypersensitivity to aspirin), an initial dose of 162 to 325 mg of nonenteric-coated aspirin (chewed and swallowed) should be given to all patients with suspected UA. Those patients allergic or intolerant to aspirin should receive clopidogrel as soon as possible. For patients who undergo PCI, aspirin at 162 to 325 mg/d is recommended for at least 1 month after bare-metal stent (BMS), 3 months after sirolimus-eluting stent implantation, and 6 months after paclitaxel-eluting stent implantation followed by 81 to 162 mg/d indefinitely thereafter. Subsequent daily aspirin doses can be reduced, with the preferred dose for secondary prevention being 81 to 162 mg daily; this should be continued indefinitely.
- 5. **Ticlopidine.** Ticlopidine was the first commercially available thienopyridine. Ticlopidine and the other thienopyridines inhibit adenosine diphosphate-induced platelet aggregation. Compared with placebo, ticlopidine reduced rates of death or MI at 6 months among patients with UA to a degree similar to that of aspirin. Ticlopidine is associated with a 1% to 5% increase in neutropenia and is thus no longer recommended as a first-line thienopyridine in patients who present with UA/NSTEMI. It is now reserved for patients in whom clopidogrel or prasugrel is not tolerated or contraindicated.
 - a. **Pharmacokinetics.** Ticlopidine's onset of action is delayed, usually taking 2 to 3 days for maximum antiplatelet effect.
 - b. **Side effects.** Ticlopidine can cause neutropenia (1% to 5% of patients) and is rarely associated with thrombotic thrombocytopenic purpura (TTP).
 - c. **Dosing.** Ticlopidine is given as a loading dose of 500 mg followed by 250 mg twice daily.
- 6. **Clopidogrel.** Clopidogrel was the second commercially available thienopyridine and is the most extensively studied member of this group. In the CURE trial, patients with UA or NSTEMI had a lower rate of cardiovascular death, nonfatal MI, or stroke when treated with aspirin and clopidogrel versus aspirin alone (9.3% vs. 11.4%, $p < 0.001$). Patients treated with this combination experienced lower rates of refractory ischemia, heart failure, or revascularization. However, an increased rate of major bleeding (3.7% vs. 2.7% for aspirin) was seen in

patients receiving clopidogrel, predominantly in those undergoing CABG. In a substudy of the CURE trial, PCI-CURE, pretreatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or urgent target-vessel revascularization at 30 days (4.5% vs. 6.4%) in patients with UA/NSTEMI undergoing PCI. Long-term treatment with clopidogrel resulted in lower rates of cardiovascular death, nonfatal MI, or revascularization, without a significant increase in major bleeding. The benefit of clopidogrel pretreatment in PCI was further confirmed in the CREDO trial in which patients receiving a 300-mg loading dose plus 1 year of 75 mg daily maintenance therapy of clopidogrel had a 26.9% relative reduction in death, nonfatal MI, or stroke at 1 year compared with those receiving only 1 month of maintenance therapy without any loading dose of clopidogrel.

- a. **Pharmacokinetics.** Clopidogrel is a prodrug that is metabolized to a pharmacologically active metabolite. Clopidogrel has a shorter onset of action than ticlopidine when 300 mg is given, with antiplatelet activity being detected within 2 hours after administration. Loading with 600 mg has been shown to have an even more rapid onset of action.
 - b. **Side effects.** Clopidogrel is generally well tolerated. Rarely, it can cause an allergic reaction typically resulting in diffuse urticaria. There have also been case reports of TTP with clopidogrel therapy.
 - c. **Dosing.** The conventional loading dose for clopidogrel has been 300 mg; however, recent evidence demonstrates a more rapid and heightened platelet inhibitory response, resulting in decreased ischemic events after PCI with use of a 600-mg loading dose of clopidogrel. The CURRENT OASIS-7 trial found that patients presenting with ACS who ultimately undergo PCI have a lower rate of cardiovascular death, MI, and stroke when loaded with 600 mg versus 300 mg. This decrease in ischemic end points came at the cost of an increase in major bleeding. Clopidogrel maintenance therapy is 75 mg daily.
7. **Prasugrel.** Prasugrel is the most recently commercially available thienopyridine. In preclinical studies, prasugrel has been shown to have a more potent antiplatelet effect than clopidogrel. The TRITON-TIMI 38 trial evaluated the efficacy of prasugrel versus clopidogrel in patients presenting with ACS with planned PCI. In this study of 13,608 patients, use of prasugrel as compared with clopidogrel resulted in a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke (9.9% vs. 12.1%, $p < 0.001$). However, the salutary benefits in reduction of ischemic events with prasugrel came at the expense of an increase in late bleeding events, including a significant increase in rates of both major bleeding (2.4% vs. 1.1%, $p = 0.03$) and fatal bleeding (0.4% vs. 0.1%, $p = 0.002$). It is an absolute contraindication to use prasugrel in patients with a history of transient ischemic attack or stroke and a relative contraindication in patients ≥ 75 years of age or < 60 kg due to the absence of a net favorable benefit or even a harmful effect in these patient subgroups.
- a. **Pharmacodynamics.** Like clopidogrel, prasugrel is a prodrug and is rapidly metabolized to a pharmacologically active metabolite and inactive metabolites. After a 60-mg loading dose of prasugrel is given, 90% of patients achieve $\geq 50\%$ inhibition of platelet aggregation within 1 hour, with maximum achieved platelet inhibition being approximately 80%. The mean steady-state inhibition of platelet aggregation with prasugrel is 70% after 3 to 5 days of treatment. Platelet aggregation returns to baseline 5 to 9 days after discontinuation of therapy.
 - b. **Side effects.** Similar to clopidogrel, prasugrel is generally well tolerated. Allergic reactions to prasugrel are rare; however, bleeding-related complications such as epistaxis or easy bruising are not uncommon.

- c. **Dosing.** The loading dose for prasugrel is 60 mg followed by a maintenance dose of 10 mg/d.
- 8. **Ticagrelor.** Ticagrelor is a recently FDA-approved reversible non-thienopyridine P2Y₁₂ receptor antagonist. Unlike clopidogrel and prasugrel, ticagrelor is not a prodrug and does not require bioactivation. In the PLATO trial involving patients presenting with ACS, there was a significant 1.9% reduction in major adverse cardiac events and a significant 1.4% reduction in death for patients who were randomized to receive ticagrelor versus clopidogrel. This came at the cost of an increase in nonprocedural bleeding in patients who were randomized to ticagrelor. In addition, dyspnea was noted in 14% of patients taking ticagrelor.
 - a. **Dosing.** The loading dose of ticagrelor is 180 mg followed by a maintenance dose of 80 mg twice daily. Ticagrelor was not FDA approved at the time of the 2011 UA/NSTEMI guidelines, and so it is not currently included in the recommendations.
- 9. **Heparin.** UFH in combination with aspirin reduces the incidence of ischemic events in patients with UA. A meta-analysis of six trials in patients with UA demonstrated that treatment with aspirin plus UFH reduced the incidence of death or nonfatal MI by 33% compared with treatment with aspirin alone, although this difference did not quite reach statistical significance. The treatment effect of heparin may also wane after therapy is discontinued.
 - a. **Duration of therapy.** Although the optimal length of therapy with UFH is unknown, studies have suggested that therapy must be continued for at least 3 to 7 days to achieve clinical benefit. Currently, heparin is discontinued after angiography and PCI are performed.
 - b. **Rebound ischemia.** Rebound ischemia is thought to result from the accumulation of thrombin during UFH administration and the ensuing platelet aggregation. Studies have shown that this rebound ischemia can be attenuated with the concomitant use of aspirin.
 - c. **Recommendations.** Intravenous UFH can be used for anticoagulant therapy in patients with NSTEMI-ACS undergoing either an invasive or conservative treatment strategy unless contraindicated (e.g., active bleeding, known hypersensitivity, and history of heparin-associated thrombocytopenia).
 - d. **Dosing.** Initially, heparin should be given as a weight-adjusted bolus (60 U/kg), followed with an infusion (15 U/kg/h). The activated partial thromboplastin time (aPTT) should be monitored every 6 hours until it stabilizes between 50 and 70 seconds and monitored subsequently every 12 to 24 hours thereafter. Standardized heparin nomograms have simplified and streamlined the initial orders for UFH and the subsequent adjustment of dosing based on aPTT levels.
- 10. **Low-molecular-weight heparin (LMWH).** The advantages of LMWH compared with UFH include increased bioavailability, a fixed dosing regimen, more effective thrombin inhibition, lower rates of heparin-induced thrombocytopenia, and cost savings because serial aPTT levels do not have to be monitored.
 - a. **Comparison with heparin.** A meta-analysis of 12 trials involving 17,157 patients with UA/NSTEMI that compared the use of several different LMWHs with UFH found no significant benefit with LMWHs compared with UFH (odds ratio [OR] = 0.88, 95% CI: 0.69 to 1.12, $p = 0.34$). In the **ESSENCE** trial, however, patients with UA/NSTEMI had a lower rate of death, MI, or recurrent angina at 30 days when treated with the LMWH, enoxaparin, than with UFH (19.8% vs. 23.3%, $p = 0.016$). Patients treated with enoxaparin also underwent fewer revascularization procedures and experienced similar rates of major bleeding. Similarly, in the **TIMI IIB** study, patients with UA/NSTEMI treated with enoxaparin had a lower rate of death, MI, or urgent revascularization at 43 days compared with those treated

- c. **Recommendations.** Fondaparinux can be used for anticoagulant therapy in those patients selected to undergo a conservative medical approach. It is the preferred therapy in patients with increased risk of bleeding being managed with medical therapy. For patients who undergo angiography and PCI, adjunctive UFH is recommended, given the increased rates of catheter-associated thrombus with fondaparinux in the **OASIS-5** trial.

13. GP IIb/IIIa inhibitors

Background. Platelet aggregation requires the activation of GP IIb/IIIa receptors on the platelet surface. The GP IIb/IIIa receptors of adjacent platelets bind fibrinogen molecules that allow cross-linking of the platelets, which subsequently initiates thrombus formation. Blocking the GP IIb/IIIa receptor inhibits platelet aggregation and reduces thrombus formation. **Abciximab**, the Fab fragment of a murine monoclonal antibody to the human GP IIb/IIIa receptor, binds this receptor tightly and inhibits platelet aggregation for days after the drug infusion is discontinued. In addition to its affinity for the GP IIb/IIIa receptor, abciximab inhibits other receptors, including the vitronectin receptor on endothelial cells and the MAC-1 receptor on leukocytes. **Eptifibatide** is a cyclic peptide inhibitor derived from snake venom, with rapid onset and a short half-life. Because of its short half-life, continuous drug infusion is required to sustain maximal inhibition of platelet aggregation. **Tirofiban** may also be utilized.

Use in UA during PCI. Abciximab and eptifibatide have been approved by the FDA for use as adjunctive therapy during PCI. Tirofiban has been approved for the treatment of UA, with continuation of its use into the catheterization laboratory.

- a. **Abciximab** was studied in patients with UA undergoing high-risk percutaneous transluminal coronary angioplasty (PTCA) in the Evaluation of 7E3 for the Prevention of Ischemic Complications (**EPIC**) trial. In 489 patients, abciximab lowered major ischemic event rates (12.8% for placebo vs. 4.8% for abciximab, $p = 0.012$) at 30 days, primarily because of a reduced rate of death or MI. This benefit was maintained at long-term follow-up (3 years). In the Evaluation in PTCA to Improve Long-term Outcome with abciximab Glycoprotein IIb/IIIa blockade (**EPILOG**) trial, treatment with abciximab in addition to heparin was associated with a significant reduction in the rate of death, MI, or urgent revascularization at 30 days (11.7% vs. 5.2% in the low-dose heparin group, $p < 0.001$), expanding the benefit to low- and intermediate-risk patients undergoing PCI. In the EPILOG trial, a lower, weight-adjusted dosing algorithm of heparin resulted in similar major and minor bleeding rates between abciximab and placebo. In the c7E3 Fab Antiplatelet Therapy for Unstable Refractory Angina (**CAPTURE**) study, abciximab given 18 to 24 hours before PCI reduced the rate of death, MI, and urgent intervention (10.8% vs. 15.4%, $p = 0.017$). Patients treated with abciximab also had a higher rate of thrombus resolution and improved procedural success. Results from the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (**EPISTENT**) trial demonstrated that when **stents and abciximab** are used together, the rate of adverse ischemic events and long-term (1-year) mortality is lower than that with stents alone. Abciximab (bolus of 0.25 mg/kg abciximab is followed by 12-hour infusion at 10 µg/min) is commonly used during PCI in patients with ACS.
- b. **Tirofiban.** In the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (**RESTORE**) trial, patients presenting with ACS who underwent PCI within 72 hours of presentation were treated with heparin and aspirin with the addition of tirofiban or placebo. Treatment with tirofiban resulted in a reduction in the short-term rate of death, MI, or revascularization for failed PTCA or recurrent ischemia without an increase in major bleeding. In the Platelet Receptor Inhibition in Ischemic Syndrome

Management (**PRISM**) trial, treatment with tirofiban (the dose used was a 0.6 µg/kg/min bolus for 30 minutes, followed by an infusion of 0.15 µg/kg/min) in patients with UA resulted in a 32% decrease in the rate of death, MI, or refractory ischemia at 48 hours (3.8% vs. 5.6%, $p = 0.01$). The composite end point, however, was not significantly different at 30 days, although the mortality was reduced (3.6% vs. 2.3%). Notably, very few patients underwent PCI during the treatment period (1.9%). In the Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (**PRISM-PLUS**) trial, tirofiban in addition to heparin was associated with a decreased rate of death, MI, or refractory ischemia compared with heparin alone at 7 days (12.9% vs. 17.9%, $p = 0.004$), at 30 days (18.5% vs. 22.3%, $p = 0.03$), and at 6 months (27.7% vs. 32.1%, $p = 0.02$).

- c. **Eptifibatide** was evaluated in the **PURSUIT** trial. Eptifibatide treatment (180 µg/kg bolus followed by an infusion of 1.3 or 2.0 µg/kg/min) in patients with UA/NSTEMI was associated with a decreased rate of death or nonfatal MI at 30 days compared with placebo (14.2% vs. 15.7%, $p = 0.04$), although with an increased rate of bleeding.
- d. **Use independently of PCI.** Eptifibatide and tirofiban have been approved for use in the care of patients with UA as a primary medical therapy whether PCI is performed or not. A pooled analysis of the **CAPTURE**, **PURSUIT**, and **PRISM-PLUS** trials revealed that during the study medication infusion, treatment with a GP IIb/IIIa inhibitor resulted in a reduction of death or nonfatal MI of 34% in patients with UA/NSTEMI, suggesting an early benefit during medical treatment that may be independent of its effect during PCI. However, in the **GUSTO IV-ACS** trial, patients with UA/NSTEMI treated with abciximab bolus and infusion for 24 or 48 hours received no benefit in addition to conventional therapy with aspirin and heparin, with the 30-day incidence of death or MI being similar across groups (8.0% placebo, 8.2% for 24-hour infusion, and 9.1% for 48-hour infusion). Medical management was encouraged during the first 48 hours, and only 1.6% of patients underwent PCI while on the study drug. In patients not likely to be treated with an early invasive strategy, abciximab has shown no benefit using the dosing protocol described in that trial.
- e. **Recommendations. The benefit of GP IIb/IIIa inhibitors is predominantly in patients who subsequently undergo PCI.** However, in the contemporary era with newer anticoagulant therapies and use of higher loading doses of clopidogrel (600 mg), there is less clarity regarding the utility of adjuvant GP IIb/IIIa inhibition with PCI. The **ISAR-REACT 2** trial randomized 2,022 patients with NSTEMI-ACS undergoing PCI to abciximab or placebo in addition to pretreatment with a 600-mg loading dose of clopidogrel. Overall, there was a 25% reduction in death, MI, or urgent target-vessel revascularization noted in those patients who received abciximab. However, this benefit was observed solely in those patients with elevated troponin levels. Also, the **ACUITY** trial suggests that GP IIb/IIIa inhibition is unnecessary in those patients who have received bivalirudin plus clopidogrel pretreatment with a loading dose of at least 300 mg at least 6 hours prior to angiography. For patients with UA/NSTEMI undergoing an **early invasive strategy**, the ACC/American Heart Association (AHA) guidelines state that either a GP IIb/IIIa inhibitor or clopidogrel can be used upstream in lower risk patients, whereas combination therapy with both is favorable in patients with high-risk features, with early recurrent ischemic discomfort, or having a delay to angiography. If PCI is likely to be performed and there is no expected delay to angiography, then abciximab can be used upstream for

GP IIb/IIIa inhibition. Otherwise, eptifibatide or tirofiban is the preferred GP IIb/IIIa inhibitor of choice.

f. Subgroups that benefit from GP IIb/IIIa inhibitors

(1) **Troponin-positive status.** Several studies have shown that the benefit of these agents resides primarily with patients presenting with elevated cardiac troponins. In the **CAPTURE** trial, patients with UA with an elevated troponin T level had a greater reduction in the rate of death or nonfatal MI with abciximab therapy than patients with a normal troponin T level. This continues to be true in the contemporary era of dual antiplatelet therapy with aspirin and clopidogrel, as discussed earlier with the results of the **ISAR-REACT 2** trial. Therefore, elevated troponin levels continue to identify patients at higher risk for adverse cardiac events who may benefit particularly from therapy with GP IIb/IIIa inhibitors.

(2) **Diabetics.** In a meta-analysis of diabetic patients with ACS, the use of GP IIb/IIIa inhibitors was associated with decreased mortality at 30 days (6.2% vs. 4.6%, $p = 0.007$). In diabetic patients with ACS undergoing PCI, treatment with GP IIb/IIIa inhibitors was associated with a more marked benefit (mortality rate: 4.0% vs. 1.2%, $p = 0.002$). In this same analysis, GP IIb/IIIa inhibitors did not confer the same improvement in mortality to nondiabetic patients (3.0% vs. 3.0%). These data suggest that diabetic patients, in particular, benefit from the use of these agents, when undergoing PCI during the initial hospitalization.

g. Oral GP IIb/IIIa inhibitors. Oral GP IIb/IIIa inhibitors have not been shown to be beneficial and may increase mortality. The reason for this dichotomy between the benefit seen with intravenous GP IIb/IIIa inhibitors and the detriment seen with oral inhibitors is not entirely clear. One possible explanation is that the oral agents, in contrast to the intravenous GP IIb/IIIa inhibitors, have partial agonist activity, which actually leads to an increase in fibrinogen binding and platelet aggregation on administration.

14. Fibrinolytic agents. Although fibrinolytic therapy has decreased mortality and improved LV function among patients with STEMI, the use of these agents is associated with worse outcomes in patients with UA and NSTEMI. A meta-analysis of fibrinolytic therapy in the management of UA demonstrated an increase in death or nonfatal MI in patients receiving fibrinolytics (9.8% for fibrinolytics vs. 6.9% for placebo). The lack of efficacy of fibrinolytic agents in these patients may result from the prothrombotic milieu induced by exposure of clot-bound thrombin after fibrin cleavage. Plasmin generation increases, and platelets are activated, perpetuating this prothrombotic state. Fibrinolytic agents would not be expected to dramatically improve coronary blood flow in UA because of the nonocclusive nature of thrombi in these patients.

VI. HOSPITAL DISCHARGE AND POSTDISCHARGE CARE. The risk of progression to MI or the development of recurrent MI or death is highest during the first two months after UA/NSTEMI. Thus, although patients with UA usually receive definitive therapy during hospitalization, close follow-up care after hospital discharge is imperative. There are no guidelines regarding noninvasive stress testing of patients without symptoms who have undergone percutaneous or surgical revascularization for UA. If anginal symptoms recur after hospital discharge, stress testing or cardiac catheterization can be performed, depending on the clinical presentation. Follow-up must include lifestyle alteration, risk factor modification, and secondary prevention. An exercise regimen in stable patients, smoking cessation efforts, and dietary changes have all been shown to improve outcomes. Hypertension, dyslipidemia, and diabetes mellitus must be diagnosed and aggressively treated. Antianginals (i.e., nitrates, β -blockers, and possibly calcium antagonists) should be used for symptom relief. Patients must be reassured and educated about their

acceptable level of activity. **The long-term use of aspirin, clopidogrel, β -blockers, statins/cholesterol-lowering regimens, and/or ACE inhibitors should not be neglected.** Specific recommendations regarding a secondary prevention postdischarge medication regimen are listed below:

- A. **Anti-ischemic medications** that were required to control symptoms during the hospitalization should be continued after discharge in patients who did not undergo coronary revascularization, had an unsuccessful revascularization, or had recurrent angina after revascularization. This will often require additional titration of the anti-ischemic medications (see Section VI.A). All patients should be given clear instructions about what symptoms to look for that are suggestive of worsening myocardial ischemia. In addition, all patients should be given **sublingual or spray nitroglycerin** and instructions on how to use it.
- B. **Aspirin 75 to 162 mg daily should be continued indefinitely for all patients who have had UA/NSTEMI.** Patients who have undergone PCI with a BMS should be given ASA 162 to 325 mg daily for at least 1 month after stent implantation. Patients who have undergone PCI with a drug-eluting stent (DES) should be given ASA 162 to 325 mg daily for at least 3 months after sirolimus-eluting stent implantation and at least 6 months after paclitaxel-eluting stent implantation, after which daily ASA at 75 to 162 mg should be continued indefinitely. For post-PCI patients in whom there is concern for a risk of bleeding, an initial lower dose of ASA at 75 to 162 mg/d is acceptable. For patients in whom ASA is contraindicated or not tolerated, clopidogrel 75 mg daily (preferred) or ticlopidine (if not contraindicated) should be given indefinitely.
- C. **Thienopyridine therapy.** In patients with UA/NSTEMI who underwent PCI with a DES or BMS, clopidogrel, ticagrelor, or prasugrel therapy should be continued for at least 12 months and further continuation beyond 15 months may be considered. In patients in whom the risk of bleeding outweighs the expected benefits of prolonged thienopyridine therapy, early discontinuation can be considered, especially in patients who have received a BMS. UA/NSTEMI patients who were treated medically without PCI should be given clopidogrel 75 mg daily for at least 1 month, and ideally up to 1 year. Although there are currently no data proving that performing **platelet function testing** on patients on thienopyridine therapy results in improved outcomes, it is considered reasonable to do so if the results of testing would alter management.
- D. **β -Blockers** should be given indefinitely to all UA/NSTEMI patients unless contraindicated. Patients recovering from UA/NSTEMI with moderate or severe LV dysfunction should be gradually titrated onto adequate β -blocker therapy. **Calcium channel blockers** (other than short-acting dihydropyridine calcium channel blockers) are recommended for ischemic symptoms when β -blockers are not successful, are contraindicated, or are not tolerated.
- E. **ACE inhibitors** should be given indefinitely to all patients with UA/NSTEMI and heart failure, left ventricular ejection fraction (LVEF) < 40%, hypertension, or diabetes mellitus unless contraindicated. An ACE inhibitor is also reasonable in UA/NSTEMI patients in the absence of these conditions. **Angiotensin receptor blockers** should be given to patients who are intolerant of ACE inhibitors and have heart failure with an LVEF < 40%.
- F. **Aldosterone receptor antagonists** should be given to post-UA/NSTEMI patients who do not have significant renal dysfunction (CrCl > 30 mL/min), do not have hyperkalemia ($K \leq 5$ mEq/L), are already on an adequate dose of ACE inhibitor, and have heart failure or diabetes mellitus with an LVEF < 40%. In the EPHEsus trial, 6,642 patients post-MI (3 to 14 days) with an LVEF \leq 40% along with either symptomatic heart failure or diabetes mellitus were randomized to oral eplerenone (starting dose of 25 mg, titrated to maximum of 50 mg/d) or placebo in addition to optimal medical therapy. In those individuals randomized to eplerenone as compared with placebo, there was a significant reduction in overall mortality (14.4% vs. 16.7%,

$p = 0.008$), cardiovascular mortality (12.3% vs. 14.6%, $p = 0.005$), and cardiovascular mortality or hospitalization for cardiovascular events (26.7% vs. 30%, $p = 0.002$) at mean follow-up of 16 months. There is an increased risk of hyperkalemia with use of this agent, particularly in those patients with abnormal renal function. In the **EPHESUS** study, there was a significant increase in the risk of serious hyperkalemia (serum potassium ≥ 6.0 mmol/L) in patients using eplerenone as compared with those in the placebo group (5.5% vs. 3.9%, $p = 0.002$). Eplerenone should not be used in those patients with severe renal insufficiency.

- G. Statin therapy** should be given to all patients with UA/NSTEMI, regardless of baseline low-density lipoprotein cholesterol (LDL-C) levels. LDL-C levels should be lowered to ≤ 100 mg/dL and to levels ≤ 70 mg/dL if feasible.

3-Hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (i.e., **statins**) have been shown to be integral in primary and secondary prevention of CAD. Early initiation of statin therapy has beneficial effects in patients with NSTEMI-ACS as well. In the **MIRACL** study involving 3,086 patients with UA/NSTEMI, treatment with atorvastatin 24 to 96 hours after presentation was associated with a decreased rate of death, nonfatal MI, cardiac arrest, or recurrent ischemia at 16 weeks (14.8% vs. 17.4%, RR = 0.84, 95% CI: 0.70 to 1.00, $p = 0.048$), primarily because of reduced recurrent symptomatic ischemia requiring hospitalization. The **PROVE IT-TIMI 22** trial demonstrated the salutary effects of aggressive lipid-lowering therapy in patients with ACS. In this study, 4,162 patients with ACS were randomized to pravastatin 40 mg daily (standard therapy) or atorvastatin 80 mg daily (intensive therapy) and followed for a mean of 24 months. There was a significant 16% reduction in the rate of death, MI, UA requiring rehospitalization, revascularization, and stroke at 2 years in those randomized to more intensive lipid-lowering therapy compared with standard lipid therapy (22.4% vs. 26.3%, $p = 0.005$). Further analysis from this trial demonstrated an early clinical benefit, which correlated with concomitant reductions in C-reactive protein levels, at 30 days with use of intensive lipid-lowering therapy. These early benefits from statin therapy are likely caused by the “pleiotropic” or nonlipid-lowering effects of statins such as their anti-inflammatory, antioxidant, and antithrombotic properties. Statins’ anti-inflammatory effects are likely responsible for beneficial effects in the periprocedural MI reduction seen in patients with NSTEMI-ACS treated with PCI. In the **ARMYDA-ACS** study of patients with NSTEMI-ACS undergoing PCI, pretreatment (12 hours prior to PCI) with atorvastatin 80 mg as compared with placebo resulted in a significant reduction in death, MI, or unplanned revascularization at 30 days (5% vs. 17%, $p = 0.01$), which was driven entirely by the reduction in periprocedural MI rates (5% vs. 15%, $p = 0.04$).

ACKNOWLEDGMENTS: *The author thanks Drs. Telly Meadows, David S. Lee, and Matthew T. Roe for their contributions to earlier editions of this chapter.*

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Complications of Acute Myocardial Infarction

I. INTRODUCTION. In-hospital mortality after acute myocardial infarction (MI) is primarily caused by circulatory failure from severe left ventricular (LV) dysfunction and/or other acute complications of MI. These complications can be broadly classified as **mechanical, arrhythmic, embolic, and inflammatory (e.g., pericarditis).**

II. MECHANICAL COMPLICATIONS. Mechanical complications of acute MI include ventricular septal rupture (VSR), acute mitral regurgitation (MR), ventricular free wall rupture, ventricular pseudoaneurysm, and ventricular aneurysm.

A. Ventricular septal rupture

1. Clinical presentation. VSR occurred in 1% to 2% of patients after acute MI in the prethrombolytic era and accounted for 5% of the periinfarction mortality. The incidence has dramatically decreased in the postthrombolytic era. In the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries 1 (GUSTO-1) trial, the incidence of VSR was approximately 0.2%, occurring with equal frequency in anterior and non-anterior locations. VSR is more likely to occur in patients who are **older, female, and hypertensive and have no prior history of smoking.** It commonly occurs in the setting of a **first MI, in the background of delayed or absent reperfusion therapy.** Angiography usually reveals an **absence of collateral circulation to the infarct zone.** VSR may develop as early as 24 hours after MI but is usually seen 2 to 5 days after MI. Fibrinolytic therapy is not associated with increased risk of VSR but may accelerate rupture in vulnerable subjects, accounting for the “early hazard” observed with treatment over placebo in randomized clinical trials.

a. Signs and symptoms. Patients with post-MI VSR may appear relatively comfortable early in the disease course. Recurrence of angina, pulmonary edema, hypotension, and shock may develop abruptly later in the course. Alternatively, precipitous onset of hemodynamic compromise characterized by hypotension, biventricular failure, and a new murmur may be the initial manifestation.

b. Physical findings. The diagnosis should be suspected when a new **pansystolic murmur** develops, especially in the setting of worsening hemodynamic profile and biventricular failure. For this reason, it is important that **all patients with MI have a well-documented cardiac examination** at presentation and frequent evaluations thereafter. This assumes critical importance as systems struggle to achieve optimal door-to-balloon times.

(1) The murmur is usually best heard at the **lower left sternal border**; it is accompanied by a **thrill in 50% of the cases.** In patients with a large

TABLE 3.1 Differential Diagnosis of a New Systolic Murmur after Acute Myocardial Infarction

Differentiating features	Ventricular septal rupture	Acute mitral regurgitation
Location of MI	Anterior = nonanterior	Inferoposterior > anterior
Location of murmur	Lower left sternal border	Cardiac apex
Intensity	Loud	Variable; may be faint
Thrill	50% of patients	Rare
RV failure	More likely	Less likely
Pulmonary edema	Less likely	More likely
V waves in PCWP	Present or absent	Almost always present
V waves in PA tracing	Absent	Present
O ₂ step-up in PA	Almost always present	Present or absent

MI, myocardial infarction; PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure; RV, right ventricular.

VSR and severe heart failure or cardiogenic shock, the murmur may be of low intensity or inaudible, but **the absence of a murmur does not rule out VSR**.

- (2) Several features differentiate the murmur of VSR from that of acute MR (Table 3.1). The murmur may radiate to the base and the apex of the heart. A third heart sound (S₃), loud P₂, and signs of tricuspid regurgitation may be present.
2. **Histopathology.** The defect usually occurs at the myocardial infarct border zone, located in the **apical septum with anterior MI** and in the **basal posterior septum with inferior MI**. A VSR almost always occurs in the setting of a transmural MI. The defect may not always be a single large defect; a meshwork of serpiginous channels can be identified in 30% to 40% of patients. Multiple fenestrations are especially common with inferior MIs.
3. **Diagnostic testing**
 - a. **An electrocardiogram** (ECG) may show atrioventricular (AV) node or infranodal conduction abnormalities in approximately 40% of patients.
 - b. **Echocardiography**
 - (1) **Transthoracic echocardiography is the test of choice** for the diagnosis of VSR. It is important for the clinician to interrogate the area of interest with color Doppler ultrasound. Lowering the Nyquist limit will enable definition and help define the size of the defect. The echocardiogram will also provide insight into the feasibility of utilizing temporizing percutaneous closure devices in this setting.
 - (a) **Basal VSR** is best visualized in the parasternal long axis with medial angulation, the apical long axis, and the subcostal long axis.
 - (b) **Apical VSR** is best visualized in the apical four-chamber view.
 - (2) In some cases, **transesophageal echocardiography** may help in determining the extent of the defect and assessing suitability for potential percutaneous closure.
 - (3) Echocardiography may help determine the size of the defect and the magnitude of the left-to-right shunt by comparing flow across the pulmonary valve with flow across the aortic valve.

- (4) An assessment of right ventricular (RV) and LV function is key to prognostication and management as they remain important determinants of mortality.
- c. **Right heart catheterization.** Pulmonary artery (PA) catheterization with oximetry measurement can help diagnose VSR by demonstrating an oxygen saturation step-up in the RV and PA. The **location of the increase is significant** because there have been case reports of enhanced oxygen saturation in the peripheral PA due to acute MR. Diagnosis involves fluoroscopically guided measurement of the oxygen saturation in the superior and inferior venae cavae; high, mid, and low right atrium (RA); base, mid, and apical levels of the RV; and the PA.
- (1) Normal oxygen saturations for these chambers are 64% to 66% in the superior vena cava (SVC), 69% to 71% in the inferior vena cava (IVC), 64% to 67% in the RA, 64% to 67% in the RV, and 64% to 67% in the PA.
- (2) An oxygen step-up at the level of the RV is characteristically seen with VSR. A left-to-right shunt across the ventricular septum typically results in a **5% or greater** increase in oxygen saturation between the RA and the RV or PA.
- (3) **Shunt fraction is calculated as follows:**

$$Q_p/Q_s = (SaO_2 - MvO_2)/(PvO_2 - PaO_2)$$

In this equation, Q_p is pulmonary flow; Q_s is systemic flow; SaO_2 is peripheral arterial oxygen saturation; MvO_2 is mixed venous oxygen saturation; PvO_2 is pulmonary venous oxygen saturation; and PaO_2 is pulmonary arterial oxygen saturation. MvO_2 is calculated by multiplying the SVC oxygen saturation by three, adding the IVC oxygen saturation, and then dividing the sum by four. PvO_2 is generally assumed to be equal to the peripheral oxygen saturation. **$Qp/Qs \geq 2$ suggests the presence of a considerable shunt. In the acute MI setting, any VSR should be considered for urgent surgical repair, regardless of the shunt fraction.**

- (4) For a patient with an intracardiac shunt, **cardiac output measured by means of the thermodilution technique is inaccurate; the Fick method should be used.** The key to measurement of accurate systemic flow in the presence of a shunt is that the oxygen content measured in the PA will be abnormally elevated and must be measured in the chamber immediately **proximal** to the shunt (i.e., the RA or the SVC and IVC in the case of VSR). The Fick equation is normally calculated as follows:
- $$\text{Cardiac output} = O_2 \text{ consumption} / [(SaO_2 - PaO_2) \times Hgb \times 1.34 \times 10]$$
- d. **Left heart catheterization.** Ventriculography performed after angiography or percutaneous intervention (PCI) may reveal VSR if the suspicion is high. Visualization is best in the left anterior oblique projection with cranial angulation.
- e. **Cardiac MRI and CT** are additional imaging modalities that can be utilized. However, the studies are more difficult to perform in hemodynamically unstable patients and do not play a significant role in this setting.
4. **Therapy**
- a. **Priority of therapy.** Urgent surgical closure is the treatment of choice (AHA/ACC class I recommendation), especially when the patient's condition is stable because hemodynamic deterioration in this setting is unpredictable. Although initial reports suggested that delaying surgery to allow healing of friable tissue improved surgical mortality, it was likely that lower mortality

was simply a result of selection bias. The mortality rate for patients with VSR treated medically is 24% at 72 hours and 75% at 3 weeks.

- b. **Vasodilators** can decrease left-to-right shunt and increase systemic flow by means of reducing systemic vascular resistance (SVR); however, a greater decrease in pulmonary vascular resistance may actually increase shunting. The vasodilator of choice is **intravenous nitroprusside**, which is started at 0.5 to 0.8 $\mu\text{g/kg/min}$ and titrated to a mean arterial pressure (MAP) of 70 to 80 mm Hg.
 - c. An **intraaortic balloon pump (IABP)** should be inserted as early as possible as a bridge to a surgical procedure, unless there is marked aortic regurgitation. IABP counterpulsation decreases SVR, decreases shunt fraction, increases coronary perfusion, and maintains blood pressure. After insertion of an IABP, vasodilators can be tailored with hemodynamic monitoring.
 - d. **Surgical therapy**
 - (1) **Cardiogenic shock and multisystem failure** are associated with high surgical mortality, further supporting earlier operations on these patients before complications develop. Mortality in patients with cardiogenic shock and VSR was 81% in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shock?) trial registry (1).
 - (2) **Surgical mortality is high** among patients with **basal septal rupture associated with inferior MI** (70% compared with 30% in patients with anterior infarcts) because of the greater technical difficulty and the need for concomitant mitral valve repair in these patients, who often have coexisting MR. RV dysfunction due to infarction and/or pressure and volume overload further increases the risk profile of these subjects.
 - e. **Percutaneous therapy.** Although surgical closure remains the treatment of choice for VSR, emerging data suggest that **percutaneous closure** may be a viable treatment for high-risk surgical patients and patients in whom surgical closure has failed. In a series of 29 patients treated with percutaneous VSR closure at a median time of 1 day after MI, mortality at 30 days in patients treated with successful device placement was 36% and 86% without and with cardiogenic shock, respectively. At a median follow-up of 730 days, mortality was 36% and 93%, respectively. In our institution, a percutaneous approach is utilized for temporary palliation and as a bridge to surgical repair only in patients considered too high risk to undergo surgery.
- B. Acute MR.** The incidence of acute MR after MI was 13% to 39% in large registries such as GUSTO-1 and SHOCK. Fibrinolytic agents decrease the overall incidence, but rupture may occur earlier in the post-MI period. MR, even if clinically silent, is a predictor of poor prognosis in MI. Multiple mechanisms may account for acute MR. These include dilation of the mitral valve annulus as a result of LV dilation; papillary muscle dysfunction with a concomitant ischemic regional wall motion abnormality near the insertion of the posterior papillary muscle; and partial or complete rupture of the chordae or papillary muscle. Severe MR caused by papillary muscle rupture is a life-threatening complication of acute MI. Historical reports indicate that papillary muscle rupture occurs between days 2 and 7. However, the SHOCK registry revealed a median time to papillary muscle rupture of 13 hours. Acute severe MR accounted for 7% of the cases of cardiogenic shock and 5% of mortality after acute MI in the SHOCK registry.
- 1. Clinical presentation**
- a. **Signs and symptoms.** These are variable and depend on the anatomy of the papillary muscle involved, the mechanism of valvular dysfunction, and the extent of injury. Complete transection of the papillary muscle is rare and usually results in immediate cardiogenic shock and death. Patients with partial or complete rupture of one or more heads of the papillary muscle lose

significant leaflet support. The resultant torrential MR can result in pulmonary edema and severe respiratory distress.

- b. **Physical findings.** A new pansystolic murmur that is audible at the cardiac apex with radiation to the axilla or the base of the heart suggests acute MR. In posterior papillary muscle rupture, the murmur radiates to the left sternal border and may be confused with the murmur of VSR or aortic stenosis. The intensity of the murmur does not predict the severity of the MR. The **murmur may often be quiet, soft, or absent** in patients with poor cardiac output or in persons with elevated left atrial pressure due to the rapid equilibration of pressures. Resting tachycardia and mechanical ventilation can also make murmur recognition challenging.
2. **Pathophysiology.** Papillary muscle rupture is **more common with an inferior MI** because the posteromedial papillary muscle receives blood supply from the posterior descending artery, whereas the anterolateral papillary muscle has dual blood supply from the left anterior descending (LAD) and circumflex arteries. Papillary muscle rupture is more likely to occur in patients with a **first MI**, and in many patients the **infarct size may be relatively small. The discordance between the degree of hemodynamic instability and the extent of myocardium in jeopardy is often a clue to the underlying condition.**
3. **Diagnostic testing**
 - a. An **ECG** usually shows evidence of recent inferior or posterior MI.
 - b. A **chest radiograph** may demonstrate pulmonary edema. In some patients, focal pulmonary edema may be seen in the right upper lobe because of flow directed at the right pulmonary veins.
 - c. **Transthoracic echocardiography** with Doppler and color flow imaging is the diagnostic modality of choice.
 - (1) The **mitral valve leaflet is usually flail** with severe MR.
 - (2) Color Doppler imaging is useful in differentiating papillary muscle rupture with severe MR from VSR after MI.
 - d. **Transesophageal echocardiography.** **Transthoracic echo may underestimate the degree of acute MR.** Rapid equalization of pressure, resting tachycardia, and poor acoustic windows may contribute to this finding. An eccentric jet in this setting should lead to the performance of **transesophageal echocardiography** to quantify the severity and elucidate the mechanism of MR.
 - e. **PA catheterization.** Hemodynamic monitoring with a PA catheter may reveal large V waves in the pulmonary capillary wedge pressure (PCWP) tracing. However, patients with VSR may also have large V waves because of increased pulmonary venous return in a normal-sized and normally compliant left atrium. Among patients with severe MR and reflected V waves in the PA tracing, **oxygen saturation in the PA may be higher** than that in the RA, complicating differentiation from VSR. There are two methods for differentiating MR from VSR:
 - (1) Prominent V waves in the PA tracing before the incisure are almost always associated with acute severe MR (Fig. 3.1).
 - (2) Blood for oximetry is obtained with fluoroscopy to ensure sampling from the main PA rather than distal branches.
4. **Therapy**
 - a. **Priority of therapy.** Papillary muscle rupture should be identified early. Patients should receive **aggressive medical therapy** and consideration for **emergent surgical repair**.
 - b. **Vasodilator therapy** is beneficial in the treatment of patients with acute MR. **Intravenous nitroprusside** decreases SVR, reduces regurgitant fraction, and increases stroke volume and cardiac output. Nitroprusside is started at 0.5 to 0.8 µg/kg/min and is titrated to an MAP of 70 to 80 mm Hg.

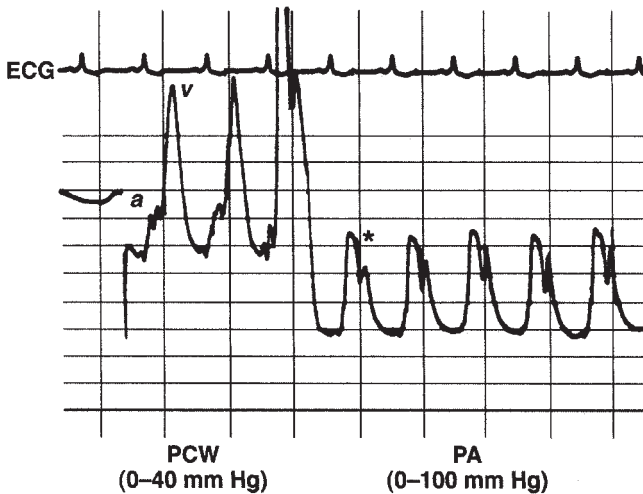


FIGURE 3.1 Giant V waves on the pulmonary capillary wedge (PCW) tracing can be transmitted to the pulmonary artery (PA) pressure, producing a notch (asterisk) on the PA downslope. (Adapted from Kern M. *The Cardiac Catheterization Handbook*. 2nd ed. St. Louis, MO: Mosby-Year Book; 1991.)

- c. **Intraaortic balloon pump.** Vasodilator therapy is contraindicated in patients with significant **hypotension** and an IABP should be inserted promptly. An IABP decreases LV afterload, improves coronary perfusion, and increases forward cardiac output. Patients with hypotension can often be given vasodilators after insertion of an IABP to improve hemodynamic values.
- d. **Percutaneous therapy.** Improvement in hemodynamic values and reduction in MR has been reported after PCI in patients with severe MR caused by papillary muscle ischemia rather than rupture. However, this is a relatively rare clinical presentation. **PCIs have no role in true papillary muscle rupture.**
- e. **Surgical therapy should be considered immediately for patients with papillary muscle rupture.**
 - (1) The prognosis is very poor among patients treated medically. Even though perioperative mortality (20% to 25%) is higher than that for elective surgical treatment, surgical therapy should be considered for every patient.
 - (2) **Coronary angiography** should be performed before surgical correction, because revascularization is associated with improved short- and long-term mortality.

C. Ventricular free wall rupture

1. **Clinical presentation.** The incidence of ventricular free wall rupture after MI in the reperfusion era is < 1%. However, ventricular free wall rupture accounts for approximately **10% of mortality after MI**. In the SHOCK registry, in-hospital mortality associated with ventricular rupture was > 60%. Rupture occurs in the

first 5 days in 50% of patients and within 2 weeks in 90% of patients. Ventricular free wall rupture occurs in the setting of a transmural MI. Risk factors include advanced age, female sex, first MI, and poor coronary collateral vessels.

a. Signs and symptoms

(1) **Acute course.** With acute rupture, patients develop tamponade, electromechanical dissociation, and sudden death. Sudden onset of chest pain with straining or coughing may suggest the onset of myocardial rupture.

(2) **Subacute course.** Some patients may have a contained rupture and present subacutely with pain suggestive of pericarditis, nausea, and hypotension. In a large retrospective analysis of post-MI patients, 2.6% of patients were found to have sustained subacute ventricular free wall rupture. Immediate bedside echocardiography may reveal localized pericardial effusion or pseudoaneurysm.

b. Physical findings. Jugular venous distention, pulsus paradoxus, diminished heart sounds, and a pericardial rub suggest subacute rupture. New to-and-fro murmurs may be heard in patients with subacute rupture or pseudoaneurysm.

2. Pathophysiology

a. Ventricular free wall rupture constitutes part of the “early hazard” of thrombolytic therapy. Mortality among patients who receive thrombolytic agents is higher for the first 24 hours and is partially attributable to ventricular rupture. Nevertheless, the overall incidence of ventricular free wall rupture is not greater in patients treated with thrombolytics. The incidence of ventricular free wall rupture is lower in patients treated with primary angioplasty compared with thrombolytics. Rupture most commonly occurs at the anterior or lateral wall, although any wall may be involved.

b. There are **three distinct types of ventricular free wall rupture** (Fig. 3.2):

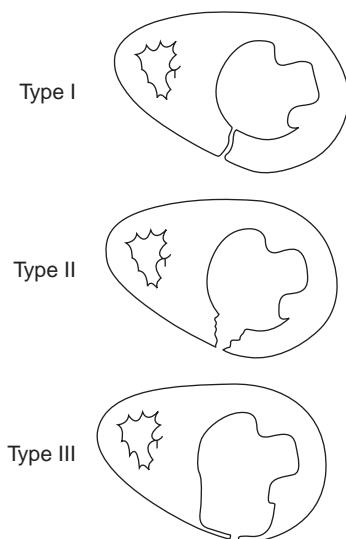


FIGURE 3.2 Morphologic classification of ventricular free wall rupture. (Reprinted with permission from Becker AE, van Mantsgem JP. Cardiac tamponade. A study of 50 hearts. *Eur J Cardiol.* 1975;3:349-358.)

- (1) **Type I** generally occurs within the first 24 hours and is a slitlike full-thickness rupture characterized by abrupt onset of symptoms (this rupture type increases with thrombolytics).
 - (2) **Type II** occurs as a result of erosion of the myocardium at the site of infarction. The rupture progresses more slowly and symptoms may be subacute.
 - (3) **Type III** occurs late and is characterized by expansion of the infarct zone with marked wall thinning and then rupture through the subsequent aneurysmal segment. It has been postulated that type III rupture occurs as a result of dynamic left ventricular outflow tract (LVOT) obstruction and the resultant increased wall stress. Type III rupture occurs less frequently in patients treated with thrombolytics.
3. **Diagnostic testing.** There may not be time for diagnostic testing in the treatment of patients with acute ventricular free wall rupture.
 - a. In addition to evidence for new MI, an **ECG** may show junctional or idioventricular rhythm, low-voltage complexes, and tall precordial T waves. A large proportion of patients have transient bradycardia immediately preceding rupture.
 - b. **Transthoracic echocardiography** reveals findings of **cardiac tamponade** in patients with a subacute course: RA and RV diastolic collapse, dilated IVC (i.e., IVC plethora), and marked respiratory variation in mitral (> 25%) and tricuspid (> 40%) inflow. Visualization of ventricular free wall rupture may be improved with echocardiographic contrast agents.
 - c. **Cardiac catheterization.** Hemodynamic evaluation with a PA catheter may reveal **equalization of the RA pressure, RV diastolic pressure, PA diastolic pressure, and PCWP** consistent with pericardial tamponade. During left heart catheterization, analysis of the arterial waveform may reveal significant **respiratory variations in the systolic blood pressure (pulsus paradoxus)**. Ventriculography performed in the right anterior or left anterior oblique orientation may allow visualization of the rupture.
 - d. **Cardiac MRI and CT** can be utilized in hemodynamically stable patients but are usually not available for critical decision making.
 4. **Therapy.** Reperfusion therapy has reduced the overall incidence of cardiac rupture.
 - a. **Priority of therapy.** The goal is to rapidly identify the problem and perform emergency surgical treatment.
 - b. **Medical therapy** has little role in the treatment of these patients, except for aggressive supportive care in anticipation of surgical correction.
 - c. **Percutaneous therapy**
 - (1) **In the setting of hemodynamic extremis, immediate pericardiocentesis** should be performed in patients with tamponade as soon as the diagnosis is made and while arrangements are being made for transport to the operating room.
 - (2) If the index of suspicion is high and the patient's condition is unstable, pericardiocentesis should be attempted without waiting for diagnostic test results.
 - (3) An indwelling catheter should be clamped and left in the pericardial cavity and connected to a drainage bag during transfer to the operating room so that continued decompression of the pericardial cavity with recurrent hemodynamic compromise can be achieved.
 - d. **Surgical therapy.** Emergency thoracotomy with surgical repair is the definitive therapy and is the **only chance for survival among patients with acute ventricular free wall rupture**.

D. Ventricular pseudoaneurysm (i.e., contained rupture)

1. **Clinical presentation.** Ventricular pseudoaneurysm is **more likely to occur with inferior MI than with anterior MI** (2).
 - a. **Signs and symptoms.** Pseudoaneurysms may remain clinically silent and be discovered during routine investigation. However, patients may present with chest pain, dyspnea, recurrent tachyarrhythmia, and sudden cardiac death.
 - b. **Physical findings.** Systolic, diastolic, or to-and-fro murmurs related to flow of blood across the narrow neck of the pseudoaneurysm during systole and diastole may be appreciated.
 2. **Pathophysiology.** Ventricular pseudoaneurysm is caused by contained rupture of the LV free wall.
 - a. The **outer walls of a true ventricular aneurysm are formed by infarcted myocardium and scar**, whereas the **outer walls of a pseudoaneurysm are formed by the pericardium and mural thrombus**. A pseudoaneurysm may remain small or undergo progressive enlargement.
 - b. Ventricular pseudoaneurysms communicate with the body of the ventricle through a **narrow neck, the diameter of which is < 50% of the diameter of the fundus**.
 3. **Diagnostic testing**
 - a. A **chest radiograph** may show cardiomegaly with an abnormal bulge on the cardiac border.
 - b. An **ECG** may demonstrate persistent ST-segment elevation, as with true aneurysms.
 - c. **Ventriculography is the most reliable method of diagnosis.**
 - d. **Echocardiography, cardiac MRI, and cardiac CT** may be utilized in evaluation as well. Echocardiographic contrast agents may increase the diagnostic accuracy.
 4. **Therapy.** Spontaneous rupture may occur without warning in approximately one-third of patients with a pseudoaneurysm. **Surgical resection is recommended for patients with or without symptoms, regardless of the size of the pseudoaneurysm, to minimize the risk of death.**
- E. Ventricular aneurysm**
1. **Clinical presentation.** The incidence of ventricular aneurysm after MI in the reperfusion era is approximately 15% and occurs **more commonly with anterior MI than with inferior or posterior MI**.
 - a. **Signs and symptoms**
 - (1) **Acute aneurysm.** Acute development of a large ventricular aneurysm can result in severe LV dysfunction and cardiogenic shock. Patients with an acute MI that involves the apex of the LV, particularly those with transmural anteroapical infarcts, are at greatest risk. Acute aneurysms expand during systole. This expansion wastes contractile energy generated by normal myocardium and puts the entire ventricle at a mechanical disadvantage.
 - (2) **Chronic aneurysms** persist > 6 weeks after MI, are less compliant than acute aneurysms, and rarely expand during systole. Patients with chronic aneurysms may experience heart failure, ventricular arrhythmias, mural thrombus, and systemic embolism, but they frequently have no symptoms.
 - b. **Physical findings.** A dyskinetic segment of the ventricle may be apparent during inspection or may be felt during palpation. The apical impulse may be displaced to the left of the midclavicular line due to cardiac enlargement. An S_3 or S_4 gallop may be appreciated due to LV dilation and stiffening. A systolic murmur of MR may occur due to changes in LV geometry.
 2. **Pathophysiology.** Infarct expansion and progressive LV dilation are consequences of absent or ineffective coronary reperfusion. The aneurysmal segment initially consists of necrotic tissue and is later replaced by fibrous scar tissue.

3. Diagnostic testing

a. ECG

(1) **Acute aneurysm.** The ECG reveals evidence of ST-segment elevation MI, which may persist despite evidence of reperfusion.

(2) **Chronic aneurysm.** ST-segment elevation that persists > 6 weeks occurs in patients with chronic ventricular aneurysms.

b. **Chest radiography** may reveal a localized bulge in the cardiac silhouette.

c. **Transthoracic echocardiography** is the diagnostic **test of choice** and accurately depicts the aneurysmal segment. It may also reveal the presence of a mural thrombus. Echocardiography is useful in differentiating a true aneurysm from a pseudoaneurysm. True aneurysms have a wide neck, whereas pseudoaneurysms have a narrow neck in relation to the diameter of the aneurysm.

d. **Cardiac MRI and CT** may also be utilized to characterize ventricular aneurysm.

4. Therapy

a. Medical therapy

(1) **Acute aneurysm.** LV failure caused by acute aneurysm is managed with **intravenous vasodilators** and **IABP** therapy. **Angiotensin-converting enzyme (ACE) inhibitors** have been shown to reduce infarct expansion and progressive LV remodeling. Because infarct expansion starts early, ACE inhibitors should be initiated within the first 24 hours of the onset of acute MI if blood pressure allows.

(2) **Chronic aneurysm.** Heart failure associated with chronic aneurysm formation is managed with afterload reduction, namely with ACE inhibitors.

(3) Anticoagulation

(a) Anticoagulation with **warfarin sodium** should be prescribed (AHA/ACC class I indication) to patients found to have a LV mural thrombus or embolic phenomenon. Patients are initially treated with intravenous heparin with a target partial thromboplastin time (PTT) of 50 to 65 seconds. Warfarin is started simultaneously. Patients should be treated with warfarin to a target international normalized ratio (INR) of 2 to 3 for at least 3 months and then indefinitely if the risk of bleeding is not excessive. Novel oral anticoagulants such as dabigatran etexilate and rivaroxaban have not been approved for this indication at this time.

(b) It is reasonable (AHA/ACC class IIa indication) to prescribe prophylactic anticoagulation to patients with LV dysfunction and extensive regional wall motion abnormalities that do not have a mural thrombus.

(c) Patients with MI requiring dual antiplatelet therapy because of PCI need to have the benefits of anticoagulation weighed against an **increase in bleeding risk with triple therapy**.

b. **Surgical therapy.** Patients with refractory heart failure and/or refractory ventricular arrhythmias should be considered for aneurysmectomy. Surgical resection may be followed by conventional closure or newer techniques (e.g., inverted T closure and endocardial patch) to maintain LV geometry.

F. **LV failure and cardiogenic shock.** Please refer to Chapter 4 for further discussion.

G. **RV failure.** Mild RV dysfunction is common after **MI of the inferior or inferoposterior wall**; however, hemodynamically significant RV impairment occurs in only 10% of patients. The **proximal right coronary artery** (RCA) is commonly involved. Extensive, irreversible RV damage is unusual because the RV has lower oxygen requirements due to its smaller muscle mass, is perfused during systole and

diastole, and often receives extensive left to right collateral blood flow. Most patients with RV infarction who survive the acute phase spontaneously improve after 48 to 72 hours.

1. Clinical presentation

- a. **Signs and symptoms.** The triad of **hypotension, jugular venous distention, and clear lung fields** is highly specific (but has poor sensitivity) for RV infarction. Patients with severe RV failure have symptoms of a low cardiac output state, including diaphoresis; cool, clammy extremities; and altered mental status. Patients often are hypotensive and oliguric. The use of **nitrates or β -blockers during routine MI treatment may precipitate profound hypotension** and provide the first clue of RV involvement. Table 3.2 lists causes of hypotension among patients with inferior wall MI.
 - b. **Physical findings.** Patients with RV failure without concomitant LV failure may have elevated jugular venous pressure (JVP) and a RV S_3 with clear lungs. The combination of JVP > 8 cm H_2O and **Kussmaul's sign** (i.e., failure of JVP to decrease with inspiration) is sensitive and specific for severe RV failure. Elevated right-sided pressures can occasionally result in **right-to-left shunting** through a patent foramen ovale. This should be considered in patients with RV infarction and hypoxia. Table 3.3 lists the clinical findings associated with an RV infarction.
- ### 2. Pathophysiology.
- RV involvement depends on the location of the RCA occlusion. Marked dysfunction occurs only if occlusion is proximal to the acute marginal branch. The degree of RV involvement also depends on the presence of left to right collateralization and the extent of diastolic reverse perfusion through the thebesian veins.

3. Diagnostic testing

- a. An **ECG** usually shows **inferior ST-segment elevation**. ST-segment elevation in **V_4R** in the setting of suspected RV infarction has a positive predictive value of 80%. RV infarction is also suggested by ST-segment elevation that is greater in lead III than lead II. ST-segment elevation exceeding 1 mm may be seen in V_1 and occasionally in V_2 and V_3 (Fig. 3.3).
- b. A **chest radiograph** is usually normal and there is no evidence of pulmonary congestion.
- c. **Transthoracic echocardiography** is the diagnostic **study of choice** for RV infarction. It may demonstrate RV dilation and severe RV dysfunction and usually shows LV inferior wall dysfunction. It is also useful in

TABLE 3.2

Causes of Hypotension in Patients Presenting with Inferior Myocardial Infarction

Right ventricular infarction
 Left ventricular failure
 Bradyarrhythmia
 Acute severe mitral regurgitation
 Ventricular septal rupture
 Bezold-Jarisch reflex

TABLE 3.3

Clinical Findings Associated with Right Ventricular Infarction

Hypotension
Elevated jugular venous pressure
Kussmaul's sign
Abnormal jugular venous pressure pattern ($y \geq x$ descent)
Tricuspid regurgitation
Right-sided S_3 and S_4
Pulsus paradoxus
High-grade atrioventricular block

differentiating RV infarction from other syndromes that can mimic it, such as cardiac tamponade.

- d. **Pulmonary artery catheterization.** Hemodynamic monitoring with a PA catheter usually reveals **high RA pressures with low PCWP**. Acute RV failure results in underfilling of the LV and a low cardiac output state. The PCWP is usually low unless concomitant, severe LV dysfunction is present. In some patients, RV dilation can cause decreased LV performance resulting from ventricular interdependence. As the RV dilates, the septum flattens or bows into the LV and restricts ventricular filling. RA pressure > 10 mm Hg and RA pressure to PCWP ratio ≥ 0.8 strongly suggests RV infarction.

4. Therapy

a. Medical therapy

- (1) **Fluid administration.** Management of RV infarction involves volume loading to increase preload and cardiac output. Some patients may require several liters in 1 hour. **Hemodynamic monitoring is crucial** because overzealous fluid administration in a patient with severe RV dilation can further decrease LV preload and cardiac output. Excessive fluid administration can cause the ventricular septum to shift toward the LV and impede LV filling. The target central venous pressure is approximately 15 mm Hg.
- (2) **Inotropes.** When volume loading fails to increase cardiac output, the use of inotropes is indicated. Administration of **dobutamine** increases cardiac index and RV ejection fraction and is superior to afterload reduction with nitroprusside.

b. Percutaneous therapy

- (1) Patients who undergo successful **reperfusion** of the RV have improved RV function and decreased 30-day mortality rates.
- (2) **AV sequential pacing** may markedly improve the condition of a patient with RV infarction and bradyarrhythmia or loss of sinus rhythm. **A longer AV delay of approximately 200 milliseconds and a heart rate of 80 to 90 beats per minute are usually optimal for these patients.**
- (3) An IABP may be beneficial, especially in cases of concomitant LV dysfunction.

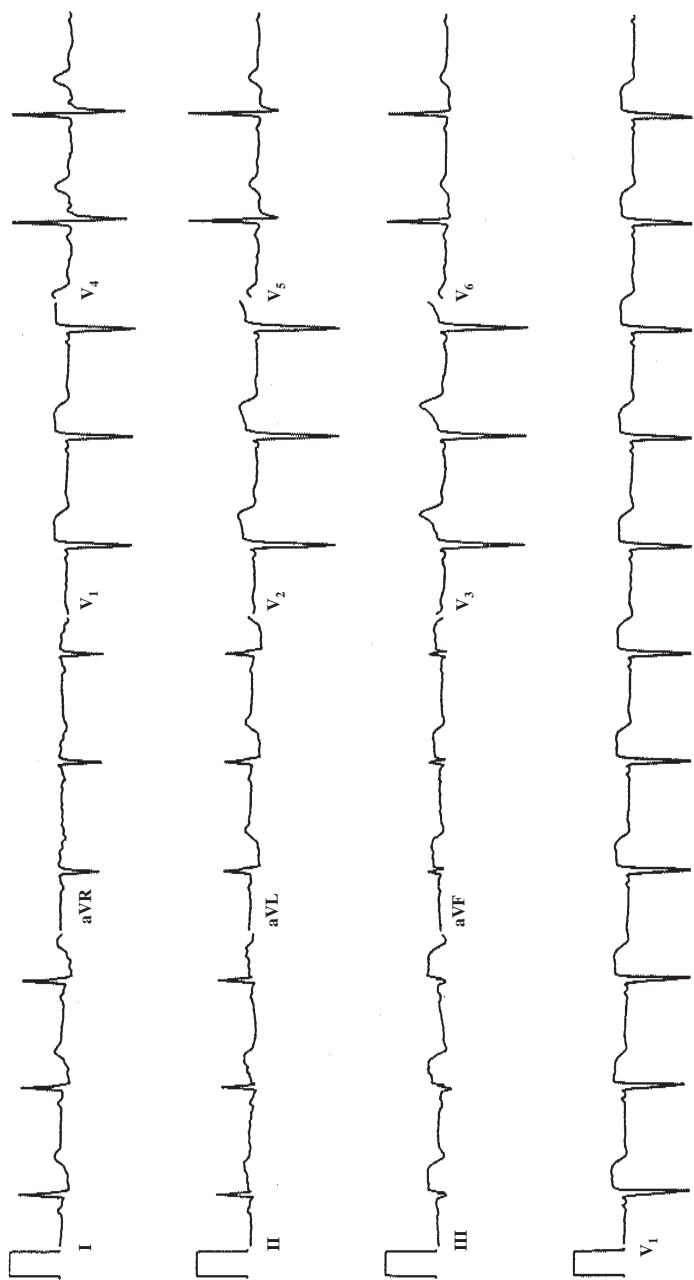


FIGURE 3.3 Electrocardiogram demonstrating acute inferior myocardial infarction with right ventricular involvement.

c. **Surgical therapy**

(1) **Pericardiectomy** may be considered in the care of patients with refractory shock as it reverses the septal impingement on LV filling.

(2) An **RV assist device** is indicated in the care of patients who remain in cardiogenic shock despite the foregoing measures.

H. Dynamic LVOT obstruction. Dynamic LVOT obstruction is an **uncommon complication** of acute anterior MI. Although this complication has been cited only in case reports, it may be an underappreciated and underreported complication.

1. **Clinical presentation**

a. **Signs and symptoms.** Patients may have respiratory distress, diaphoresis, and cool, clammy extremities in addition to the typical signs and symptoms of acute MI. Patients with severe obstruction may appear to be in cardiogenic shock, with severe orthopnea, dyspnea, and oliguria in addition to altered mental status from cerebral hypoperfusion.

b. **Physical findings** frequently include a new systolic ejection murmur heard best at the left upper sternal border with radiation to the neck. A new systolic murmur can be heard at the apex with radiation to the axilla, as a result of systolic anterior motion (SAM) of the mitral leaflet. An S_3 gallop, pulmonary rales, hypotension, and tachycardia may also occur.

2. **Pathophysiology.** The dynamic LVOT obstruction that may occur as a complication of acute anterior MI is related to compensatory hyperkinesis of the basal and mid segments of the LV. The increased contractile force of these regions decreases the cross-sectional area of the LVOT. The resultant increase in velocity of blood through the outflow tract can produce decreased pressure below the mitral valve and cause anterior mitral valve leaflet displacement toward the septum (i.e., Venturi effect). This results in further outflow tract obstruction and MR. It has been postulated that this complication can play a role in ventricular free wall rupture. LVOT obstruction leads to increased end-systolic intraventricular pressure, which leads to increased stress of the weakened, necrotic infarcted zone.

3. **Diagnostic testing.** **Transthoracic echocardiography** is the diagnostic test of choice and helps evaluate the hyperkinetic segments, the LVOT obstruction, and the presence of systolic SAM of the mitral leaflet.

4. **Medical therapy** is focused on decreasing myocardial contractility and heart rate while expanding intravascular volume and increasing afterload modestly.

a. **β -Blockers** should be added slowly and with careful monitoring of the heart rate, blood pressure, and cardiac output.

b. **Intravenous hydration** should be initiated with several small (250 mL) boluses of normal saline to increase preload and decrease LVOT obstruction and SAM. The patient's hemodynamic and respiratory status should be monitored closely during this therapeutic intervention.

III. ARRHYTHMIC COMPLICATIONS. Arrhythmias are a common complication after acute MI and are associated with significant mortality. Please refer to Chapters 21 through 25 and 41 for further discussion.

IV. EMBOLIC COMPLICATIONS. The contemporary incidence of LV mural thrombus after acute MI is approximately 5% and the incidence of systemic embolism in patients with LV mural thrombus is approximately 13%. The incidence of mural thrombus in patients with a **large anterior wall MI** is approximately 10%. Other factors associated with LV mural thrombus include **decreased LV ejection fraction, wall motion abnormalities, and LV aneurysm**.

A. Clinical presentation

1. **Signs and symptoms.** The most common clinical presentation of an embolic complication is stroke, although patients may have limb ischemia, renal infarction, and intestinal ischemia. Most episodes of systemic embolization occur in the first 2 weeks after acute MI.
 2. **Physical findings.** The physical findings depend on the site of embolism.
 - a. Patients with stroke present with neurologic deficits.
 - b. Embolism to the peripheral circulation results in limb ischemia and cold, pulseless, and painful extremities.
 - c. Renal infarctions may cause hematuria and flank pain.
 - d. Mesenteric ischemia causes abdominal pain and bloody diarrhea.
 3. **Diagnostic testing**
 - a. **Transthoracic echocardiography** is the initial diagnostic test of choice to evaluate for LV mural thrombus. Echocardiographic contrast agents may increase the diagnostic accuracy.
 - b. **Cardiac MRI** has similar specificity but may be more sensitive than echocardiography in the detection of an LV mural thrombus.
- B. Therapy** with anticoagulation is outlined above in the management of ventricular aneurysm.

V. INFLAMMATORY COMPLICATIONS

- A. Early pericarditis.** The incidence of early pericarditis after acute MI is approximately 10%. The inflammation usually develops 24 to 96 hours after MI.
1. **Clinical presentation.** Early pericarditis occurs in patients with transmural MI. A transient pericardial friction rub may be audible in some patients before symptoms become prominent.
 - a. **Signs and symptoms**
 - (1) Patients report progressive, severe chest pain that lasts for hours. The **pain is postural**: worse when the patient is supine and alleviated if the patient sits up and leans forward. The pain is usually pleuritic in nature and is worsened with deep inspiration, coughing, and swallowing.
 - (2) **Radiation of pain to the trapezius ridge** is nearly pathognomonic for acute pericarditis and does not occur in patients with ischemic pain. The pain may also radiate to the neck and less frequently to the arm or back.
 - b. **Physical findings.** The presence of a pericardial friction rub is pathognomonic for acute pericarditis; however, it can be evanescent.
 - (1) The rub is best heard at the left lower sternal edge with the diaphragm of the stethoscope.
 - (2) The rub has three components: one component each in atrial systole, ventricular systole, and ventricular diastole. In about 30% of patients, the rub is biphasic, and in 10% it is uniphasic.
 - (3) The development of pericardial effusion may cause fluctuations in the intensity of the rub, although the rub may still be heard despite substantial pericardial effusion.
 2. **Etiology and pathophysiology.** Pericarditis typically results from an area of localized pericardial inflammation overlying the infarcted myocardium. The inflammation is fibrinous in nature. The development of an evanescent pericardial rub correlates with a larger infarct and hemodynamic derangements.

3. Diagnostic testing

- a. An **ECG** is the most useful test in the diagnosis of pericarditis; however, evolving electrocardiographic changes may make the diagnosis difficult for patients who have had MI. Unlike ischemia, in which the changes are limited to a particular territory, pericarditis produces generalized electrocardiographic changes.
 - (1) The ST-segment elevation seen with pericarditis is a concave upward or saddle-shaped curve.
 - (2) In pericarditis, T waves become inverted after the ST segment becomes isoelectric, whereas in acute MI, T waves may become inverted when the ST segment is still elevated.
 - (3) Four phases of electrocardiographic abnormality have been described in association with pericarditis (Table 3.4).
- b. **Chest radiography** is of limited value in the diagnosis of pericarditis.
- c. **Echocardiography** may reveal pericardial effusion, which strongly suggests pericarditis, although the absence of effusion does not rule out the diagnosis.

4. Therapy

- a. **Aspirin** is used to manage post-MI pericarditis and doses as high as 650 mg every 4 to 6 hours may be needed.
 - b. **Nonsteroidal antiinflammatory agents and corticosteroids should not be used to treat these patients.** These agents may interfere with myocardial healing and contribute to infarct expansion.
 - c. **Colchicine** may be beneficial. Colchicine 0.6 mg every 12 hours plus conventional therapy with aspirin decreases symptom recurrence in patients with idiopathic pericarditis.
- B. Late pericarditis (i.e., Dressler's syndrome).** The incidence of Dressler's syndrome is between 1% and 3%. The syndrome occurs 1 to 8 weeks after MI. The pathogenesis is unknown, but an autoimmune mechanism has been suggested.
1. **Clinical presentation.** Patients may present with chest discomfort that suggests pericarditis, pleuritic pain, arthralgia, malaise, fever, pericardial friction rub, elevated leukocyte count, and an elevated sedimentation rate. Echocardiography may reveal a pericardial effusion.
 2. **Therapy** is similar to that for early post-MI pericarditis: aspirin, colchicine, and avoidance of nonsteroidal antiinflammatory drugs and corticosteroids. However, if > 4 weeks have elapsed since the MI, nonsteroidal antiinflammatory agents and corticosteroids may be indicated for severe symptoms.

TABLE 3.4 **Electrocardiographic Changes of Pericarditis**

Stage I	ST elevation, upright T waves
Stage II	ST elevation resolves, upright to flat T waves
Stage III	ST isoelectric, inverted T waves
Stage IV	ST isoelectric, upright T waves

ACKNOWLEDGMENTS: *The authors would like to thank Dr. David Tschopp, Dr. John Galla, and Dr. Debabrata Mukherjee for their contributions to earlier editions of this chapter.*

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CHAPTER

4

Michael P. Brunner
Venu Menon

Cardiogenic Shock Complicating Acute Myocardial Infarction

- I. INTRODUCTION.** Left ventricular (LV) dysfunction is common after acute myocardial infarction (MI), and the severity of dysfunction correlates with the extent of myocardial injury. Cardiogenic shock is estimated to **complicate 3% to 8% of cases of acute MI** (1–3). **The mortality associated with cardiogenic shock in patients with acute MI had historically approached 80%** (1,4). Despite advancements in coronary reperfusion, **the contemporary mortality associated with MI complicated by cardiogenic shock remains at 40% to 70%** (3,5,6). **Prior MI, older age, female sex, diabetes, and anterior infarction** are risk factors for the development of cardiogenic shock after MI.

II. CLINICAL PRESENTATION. Cardiogenic shock is a clinical condition in which **inadequate tissue perfusion is the consequence of cardiac dysfunction**. It is characterized by a **reduction in cardiac output despite adequate filling pressures**. Criteria typically used to define cardiogenic shock include **systolic blood pressure < 90 mm Hg** for at least 30 minutes or need for vasopressor or intra-aortic balloon support to maintain systolic blood pressure > 90 mm Hg, **pulmonary capillary wedge pressure (PCWP) > 15 mm Hg**, and **cardiac index < 2.2 L/min/kg/m²**.

A. Symptoms. Patients in cardiogenic shock from LV failure typically present with **respiratory distress**. **Confusion** may occur due to inadequate tissue perfusion.

B. Physical findings

1. **Hypotension, tachycardia, confusion, diminished urine output (<30 mL/h), and cool, mottled, and cyanotic extremities** typically characterize the clinical presentation of cardiogenic shock. Peripheral pulses are often diminished in cardiogenic shock due to decreased pulse pressure (**pulsus parvus**). In a failing left ventricle the strength of every other beat may alternate, a phenomenon known as **pulsus alternans**. A **dyskinetic segment of the ventricle** may be apparent during inspection or may be felt during palpation. An **S₃ gallop** may be heard in patients with poor LV function.
2. Patients with acute mechanical complications of MI such as ventricular septal rupture, acute mitral regurgitation, ventricular free wall rupture, ventricular pseudoaneurysm, ventricular aneurysm, right ventricular failure, and dynamic outflow tract obstruction may present with additional physical findings as discussed in Chapter 3.
3. Cardiogenic shock due to LV failure may cause pulmonary congestion and inspiratory rales. However, **a significant proportion of patients in the SHOCK (SHould we emergently revascularize Occluded coronaries for Cardiogenic shock?) registry had no pulmonary congestion** (7). Neither auscultation nor chest radiograph detected pulmonary edema in 28% of the patients.
4. A select group of patients may exhibit **preshock**. This clinical entity is characterized by signs of hypoperfusion with resting tachycardia but not frank hypotension due to a compensatory increase in systemic vascular resistance. On right heart catheterization, these patients have an ineffective cardiac index and are at high risk for in-hospital mortality.

III. RISK STRATIFICATION

- A.** In the prereperfusion era, **Killip and Kimball** classified **four subsets of patients on the basis of clinical presentation and physical findings** at the onset of MI (4). They reported an 81% in-hospital mortality in patients with cardiogenic shock (Killip class IV). In the fibrinolytic era, the 30-day mortality rate for patients in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries 1 (GUSTO-1) trial that presented with cardiogenic shock was 58% (Table 4.1) (8). The presence of resting tachycardia and pulmonary congestion identifies patients at highest risk even in the current reperfusion era.
- B.** In a classic study performed in the prereperfusion era, **Forrester** classified **four hemodynamic subsets of patients on the basis of PCWP and cardiac index** (Table 4.2) and determined the associated mortality in acute MI (9).
- C.** Right heart catheterization hemodynamic parameters including stroke volume, cardiac output, and cardiac index are strong predictors of in-hospital mortality in patients presenting with MI complicated by cardiogenic shock. In the SHOCK registry, the **cardiac power index** (mean arterial pressure \times cardiac index/451) in W/m² was the strongest independent hemodynamic correlate of in-hospital mortality (10).
- D.** The SHOCK trial investigators have also published a **severity scoring system** to predict in-hospital mortality in patients with acute MI complicated by cardiogenic

TABLE 4.1 30-Day Mortality Based on Hemodynamic (Killip) Class in the GUSTO-1 Trial

Killip class	Characteristics	Patients (%)	Mortality rate (%)
I	No evidence of CHF	85	5
II	Rales, ↑ JVD, or S ₃	13	14
III	Pulmonary edema	1	32
IV	Cardiogenic shock	1	58

CHF, congestive heart failure; ↑, increased; JVD, jugular venous distention.

Adapted from Fox AC, Glassman E, Isom OW. Surgically remediable complications of myocardial infarction. *Prog Cardiovasc Dis.* 1979;107:852-855.

shock (11). Age, shock on admission, clinical evidence of end-organ hypoperfusion, anoxic brain damage, systolic blood pressure, prior coronary artery bypass grafting, anterior MI location, and creatinine > 1.9 mg/dL are the risk factors utilized in a multivariable model. In patients with hemodynamic monitoring, age, end-organ hypoperfusion, anoxic brain damage, stroke work, and left ventricular ejection fraction < 28% are the variables considered.

IV. ETIOLOGY. Table 4.3 outlines the various etiologies of cardiogenic shock complicating acute MI. Patients with acute MI and cardiogenic shock typically have significant **left main** and **severe three-vessel coronary artery disease** and commonly have substantial involvement of the **left anterior descending artery** (12). Autopsy studies have revealed that at least 40% of the LV is affected in most patients presenting with cardiogenic shock complicating acute MI (13). Forty percent of patients have a history of prior MI. If the previous MI was large, even a small, acute MI in a nonanterior location may cause shock. **In the SHOCK registry, LV failure (79%), severe mitral regurgitation (7%), ventricular septal rupture (4%), right ventricular failure (3%), and ventricular free wall rupture (1%) were the leading causes of cardiogenic shock in acute MI** (6). **Bradycardias and tachyarrhythmias** related to acute MI can also cause cardiogenic shock. **Medications** administered for acute MI such as β-blockers, angiotensin-converting enzyme inhibitors, and morphine can cause iatrogenic shock by inducing hypotension.

TABLE 4.2 Forrester Classification

Subset	PCWP	Cardiac index	Mortality rate
I	<18	>2.2	3
II	>18	>2.2	9
III	<18	<2.2	23
IV	>18	<2.2	51

PCWP, pulmonary capillary wedge pressure.

TABLE 4.3 **Causes of Cardiogenic Shock Complicating Acute Myocardial Infarction**

Left ventricular failure
Right ventricular failure
Ventricular septal rupture
Acute mitral regurgitation
Ventricular aneurysm
Ventricular free wall rupture
Cardiac tamponade
Dynamic left ventricular outflow tract obstruction
Arrhythmia
Iatrogenic (e.g., β -blocker related)

In the Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), early β -blocker use was associated with an increased risk of developing cardiogenic shock, especially when used within the first day of admission (14). **Occult bleeding** resulting from antiplatelet and anticoagulation therapies in acute MI can also result in hypotension and circulatory collapse.

V. PATHOPHYSIOLOGY. Ineffective cardiac output in the setting of cardiogenic shock results in hypotension and tachycardia. A compensatory increase in systemic vascular resistance may occur through peripheral vasoconstriction in an effort to maintain blood pressure and tissue perfusion. However, this classic paradigm has been challenged. Data from the SHOCK registry revealed that many patients with cardiogenic shock instead had low systemic resistance, similar to patients with septic shock (15). It has been postulated that a systemic inflammatory response-like syndrome with a low systemic vascular resistance may be encountered in up to one-fifth of patients with acute MI complicated by cardiogenic shock (16). Figure 4.1 provides an overview of the pathophysiology of cardiogenic shock caused by acute MI and the expansion of the paradigm to include the contribution of inflammatory mediators.

VI. LABORATORY EXAMINATION. Decreased mixed venous oxygen saturation, lactic acidosis, and elevated creatinine and liver transaminase levels are common.

VII. DIAGNOSTIC STUDIES

- A. Electrocardiogram.** Patients with cardiogenic shock resulting from LV failure usually have extensive electrocardiographic abnormalities consistent with massive infarction, severe diffuse ischemia, or evidence of a large, prior MI. Extensive ST-segment deviations are common. Both ST-elevation MI and non-ST-elevation MI can manifest as cardiogenic shock.
- B. Chest radiography** may reveal pulmonary congestion.
- C. Hemodynamic monitoring** with an **arterial line** and **pulmonary artery (PA) catheter** is helpful in monitoring the patient's hemodynamic status and may also identify complications of acute MI, including right ventricular infarction, acute mitral regurgitation, and ventricular septal rupture. In GUSTO-1, mortality among patients ($n = 995$) presenting with acute MI and cardiogenic shock that were managed with

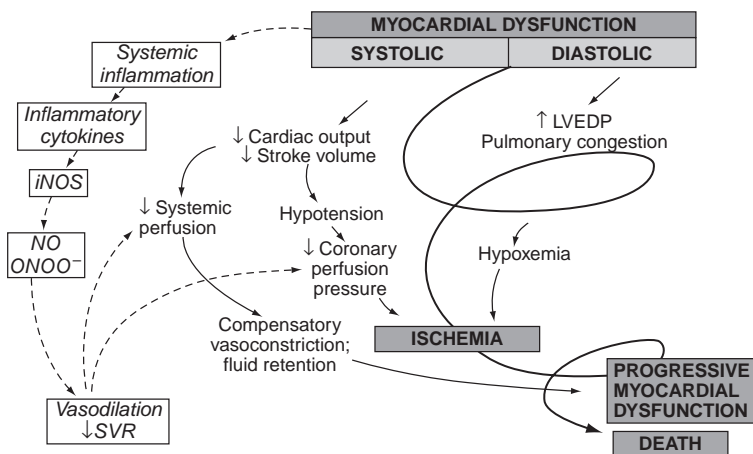


FIGURE 4.1 Expansion of the pathophysiologic paradigm of cardiogenic shock to include the potential contribution of inflammatory mediators. LVEDP, left ventricular end diastolic pressure; NO, nitric oxide; iNOS, inducible nitric oxide synthase; ONOO⁻, peroxynitrite; SVR, systemic vascular resistance. (Reprinted with permission from Hochman JS, Ohman EM. Pathophysiology. In: *Cardiogenic Shock*. Oxford: Wiley-Blackwell; 2009.)

PA catheters (45.2%) was less than among those ($n = 1,406$) that were not managed with PA catheters (63.4%) (17). However, the difference in part may be attributable to survivor bias as well as confounding.

- D. Transthoracic echocardiography** may help determine the etiology of shock as well as the extent of myocardial injury. It can identify the complications of acute MI that contribute to cardiogenic shock. It may also draw attention to additional causes of cardiogenic shock such as aortic dissection, cardiac tamponade, or pulmonary embolism.

VIII. THERAPY

- A. Priority of therapy.** Early revascularization is critically important in the management of patients presenting with acute MI and cardiogenic shock. The benefits of this strategy were proven in the SHOCK trial (18). Early revascularization saved 13 lives per 100 treated at 1 year compared with a strategy of medical stabilization and delayed revascularization. This strategy should be strongly considered in all patients aged < 75 years in the absence of contraindications; select older patients with good premonitory functional status also derived a similar benefit from this approach. Consequently, patients with acute MI complicated by cardiogenic shock should undergo prompt angiography for defining coronary anatomy. Subsequent revascularization should be guided by clinical presentation, extent of disease, and concomitant valvular function.
- B. Percutaneous coronary intervention (PCI)** of the infarct-related artery should be attempted emergently in this population. With the adoption of PCI, there has been a marked decline in the mortality of patients with acute MI complicated by cardiogenic shock. Persistence of shock following successful PCI of the infarct-related artery may be an indication to consider multivessel intervention, especially when remote ischemia in noninfarct distributions is suspected.

C. Coronary artery bypass grafting. Emergency surgical revascularization should be considered in the care of patients with severe multivessel disease or substantial left main coronary artery stenosis. It is also indicated when there is a significant concomitant valvular disease that is contributing to hemodynamic instability. Despite sicker patients with more extensive coronary artery disease being referred for coronary artery bypass grafting, mortality due to surgery in the SHOCK Trial and Registry was comparable to that of PCI. However, at many centers, there is reluctance to operate on patients in cardiogenic shock and early reperfusion is generally performed utilizing PCI.

D. Adjunctive support

1. An **intra-aortic balloon pump** (IABP) should be inserted as soon as possible in a patient with cardiogenic shock to ensure hemodynamic stability and protect end-organ perfusion. IABP support reduces afterload, improves cardiac output, and decreases the myocardial oxygen requirement by means of reduction in wall stress. An IABP is also beneficial in MI because diastolic augmentation may increase coronary perfusion in vessels that do not have a flow-limiting stenosis. Contraindications to placement include the presence of significant peripheral vascular disease, aortic dissection, and more than moderate aortic insufficiency. There are no randomized controlled trials to support the placement of an IABP in this setting. One must, however, remember that the IABP was an integral component of the early revascularization strategy observed in the SHOCK trial.
2. **Transvenous pacing.** Patients with inadequate heart rate due to bradyarrhythmia or chronotropic incompetence may require temporary pacing to increase the heart rate and augment cardiac output. **Atrial pacing** maintains atrioventricular synchrony and normal LV contraction and is preferable to ventricular pacing if atrioventricular conduction is intact.

E. Medical therapy

1. **Vasopressors.** Patients may need vasopressors to maintain an effective mean arterial pressure. **Dopamine** is started at 3 $\mu\text{g/kg/min}$ and titrated to a maximal dose of 20 $\mu\text{g/kg/min}$. **Norepinephrine** is started at 2 $\mu\text{g/min}$ and titrated to a maximal dose of 30 $\mu\text{g/min}$. Dopamine may be associated with higher mortality in cardiogenic shock than norepinephrine when titrated to maintain an effective mean arterial pressure (19).
2. **Inotropic agents.** Patients with severe LV failure and cardiogenic shock may require temporary support with an inotropic agent.
 - a. **Dobutamine** has a positive inotropic action comparable to that of dopamine and may decrease afterload. Dobutamine is started at a dose of 2.5 $\mu\text{g/kg/min}$ and increased to a maximal dose of 40 $\mu\text{g/kg/min}$.
 - b. **Milrinone**, a phosphodiesterase inhibitor with inotropic and vasodilator action, may be beneficial in some patients, especially those with right ventricular dysfunction. Milrinone is given as a 50- $\mu\text{g/kg}$ bolus over 10 minutes, followed by an infusion of 0.375 to 0.75 $\mu\text{g/kg/min}$. The bolus may be omitted in the care of patients with low blood pressure. Patients without adequate blood pressure may not tolerate milrinone.
 - c. **Levosimendan** is an intravenous agent that increases inotropy by binding cardiac troponin C and sensitizing myofilaments to calcium. It is currently approved for use in some countries in Europe and South America but is not available for use in the United States.
3. **Vasodilators** such as **nitroglycerin** and **sodium nitroprusside** can play an important role in the management of post-MI LV failure by means of preload and afterload reduction. However, in the setting of cardiogenic shock, their use may be limited by refractory hypotension.
4. Table 4.4 summarizes the hemodynamic effects of medications used in the management of cardiogenic shock.

TABLE 4.4 Hemodynamic Effects of Medications Used to Manage Cardiogenic Shock

Medication	Preload	Afterload	Inotropy	Chronotropy
Dopamine (3–10 µg/kg/min)	0	–	++++	++
Dopamine (>10 µg/kg/min)	0	+++	+++	+++
Norepinephrine (2–300 µg/min)	0	++++	+	++
Epinephrine (0.05–1 µg/kg/min)	0	+++	+++	+++
Phenylephrine (0.5–15 µg/kg/min)	0	++++	0	–
Dobutamine (2.5–25 µg/kg/min)	–	–	++++	+++
Milrinone (0.375–0.75 µg/kg/min)	– –	– –	+++	+
Nitroglycerin (2.5–300 µg/min)	– – –	–	0	+
Nitroprusside (0.3–10 µg/kg/min)	– – –	– – –	0	+

0, no effect; –, decrease; +, increase.

IX. MANAGEMENT OF REFRACTORY SHOCK AFTER CORONARY REVASCULARIZATION

- A. **Triage.** Patients that remain in cardiogenic shock despite coronary revascularization are best served by transfer to a facility that can provide additional adjunctive hemodynamic therapies. In addition, the facility should have an active cardiac transplant program and full-time availability of interventional cardiology, electrophysiology, cardiothoracic surgery, and neurology services.
- B. **Decision making.** The prognosis for patients that remain in cardiogenic shock after coronary revascularization is extremely poor. However, there are patients that do ultimately recover their LV function and survive. It is often impossible to predict which patients will do well and which patients will succumb to their illness. In our institution, we often consider additional adjunctive hemodynamic therapies as a bridge to decision making.
- C. **Additional adjunctive hemodynamic support**
 1. **Percutaneous ventricular assist device (pVAD).** Traditional mechanical circulatory support from an IABP may prove insufficient in certain patients, and consideration may be given to more aggressive support with a percutaneous assist device, especially if shock persists after coronary revascularization.
 - (a) The **TandemHeart** (Fig. 4.2) device provides left atrial to femoral artery bypass flow at rates of up to 5.0 L/min with percutaneous access and can serve as a bridge to recovery or more definitive therapy. Limited case series from isolated centers suggest that the TandemHeart device is able to rapidly reverse the terminal hemodynamic compromise seen in patients with severe cardiogenic shock refractory to IABP and/or high-dose vasopressor support (20).
 - (b) The **Impella** intracardiac axial flow ventricular assist device can provide either 2.5 or 5.0 L/min support. Our experience has been that the Impella 2.5 L/min device does not provide much additional benefit beyond that of an IABP, whereas the 5.0 L/min device provides substantial adjunctive support. Currently, the Impella 5.0 L/min device requires surgical cut-down for vascular access.

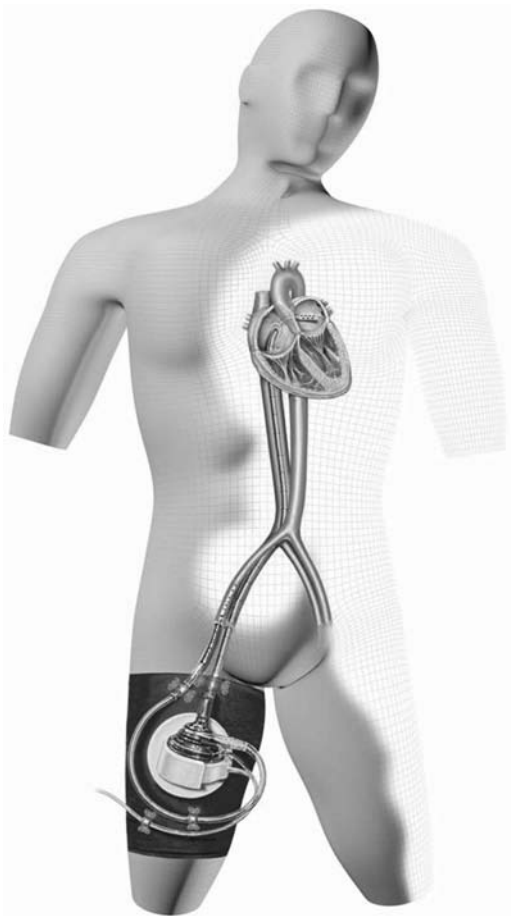


FIGURE 4.2 The TandemHeart percutaneous left ventricular assist device. (Reprinted with permission from CardiacAssist, Inc.)

2. **Extracorporeal membrane oxygenation (ECMO).** ECMO is an established therapy that can be implemented expeditiously in experienced hands. It provides hemodynamic support and as an additional advantage can support oxygenation if the lung function is compromised. We often use ECMO in our institution as a bridge in deciding whether to use more long-term therapy such as an implanted left ventricular assist device (LVAD).
3. **Left ventricular assist device.** Surgical LVAD therapy is often utilized in advanced LV failure as a destination therapy or as a bridge to transplant. In patients presenting with acute MI complicated by cardiogenic shock, LVAD therapy is a consideration. However, other temporizing measures such as pVAD or ECMO are often considered first.

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Post–Myocardial Infarction Risk Stratification and Management

- I. **INTRODUCTION.** More than 1.5 million patients will have an acute coronary syndrome (ACS) in the United States each year. At least 1 million will have evidence of myocardial infarction (MI), for which mortality and morbidity remain considerable. Although patient outcomes have improved, well-documented therapies are still often underprescribed. Besides identifying patients with MI, the goals of the physician must be to successfully stratify patients according to risk, implement medical interventions, and initiate risk factor modification during the initial hospitalization.
- II. **RISK STRATIFICATION.** Post-MI risk stratification identifies patients at high risk for subsequent cardiovascular events who will benefit from revascularization.
 - A. **Age** is the most important predictor of mortality after MI. The average age of patients with first MI is approximately 65 years. Although older patients are at greatest risk and may benefit most, they receive less aggressive treatment compared with younger patients, who have the lowest overall mortality.
 - B. **Assessment of left ventricular (LV) function**
 1. **LV function** is the second most important predictor of mortality after MI. An inverse relation exists between left ventricular ejection fraction (LVEF) and mortality. Mortality is greatest for patients with an LVEF < 40%.
 2. Assessment of LV function is indicated for all patients diagnosed with MI. Echocardiography is often utilized to assess LV function because it is readily available, is relatively inexpensive, and can assess concomitant valvular function as well as mechanical complications of MI. Left ventriculography performed during diagnostic catheterization, or ascertained by radionuclide ventriculography, and cardiac magnetic resonance may also be utilized to evaluate LV function. Availability, local expertise, and cost are important considerations when deciding which procedure to use.
 - C. **Other indicators.** Biomarkers are useful in further risk-stratifying patients after MI. **Cardiac troponin** elevation identifies high-risk patients and incremental increases in troponin levels predict higher mortality in patients with ACS. Elevated serum levels of high-sensitivity **C-reactive protein** and **B-type natriuretic peptide** may also provide prognostic information. New **ST-segment changes**, both elevation and depression, portend higher risk of death, heart failure, recurrent ischemia, and severe coronary artery disease (CAD). **Electrical instability**, such as ventricular arrhythmias and atrial fibrillation, are associated with increased risk. Anterior MI, renal insufficiency, poor glycemic control, and anemia are also associated with worse outcomes.
 - D. **Risk models.** Various models utilize a combination of the aforementioned risk factors to quantitate a predictive score of patient risk for subsequent cardiac events

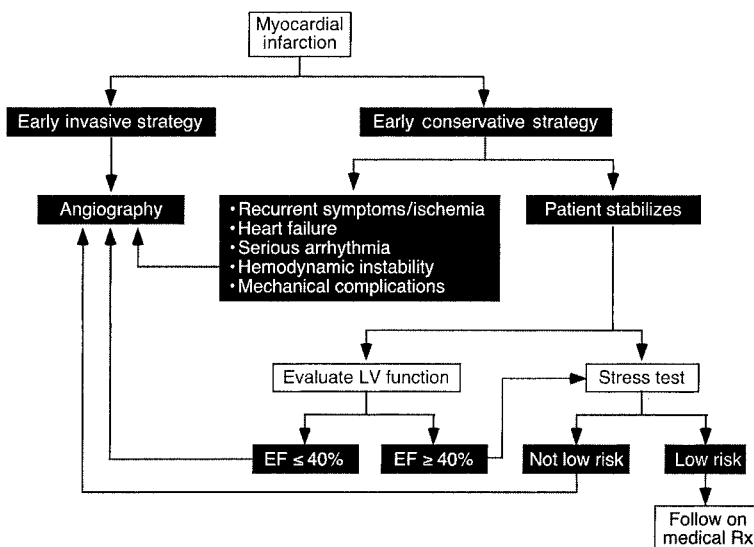


FIGURE 5.1 Post-myocardial infarction risk stratification. LV, left ventricular; EF, ejection fraction.

and mortality. Examples include Thrombolysis in Myocardial Infarction (TIMI), Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardio (GISSI), and the Global Registry of Acute Coronary Events (GRACE).

- E. Assessment of residual ischemia** (Fig. 5.1). The extent of CAD and the presence of residual ischemia are two strong predictors of mortality among patients who have had an MI. For this reason, post-MI patients who have not undergone angiography should undergo stress testing before discharge or shortly thereafter (preferably within 3 to 7 days post-MI). Non-ST-elevation ACS patients at low or intermediate risk who do not have ongoing ischemia or heart failure for at least 12 to 24 hours are also candidates for submaximal stress testing. Because of increasing availability of percutaneous revascularization and growing implementation of a pharmaco-invasive strategy for ST-elevation MI (STEMI) patients who receive thrombolytics, most patients with STEMI undergo angiographic definition. Stable STEMI patients who have not undergone catheterization should undergo stress testing to assess for ischemia 2 to 3 days after the index event.

- 1. Submaximal exercise stress testing is optimal for noninvasive risk stratification.** This test provides considerable prognostic information, assesses functional capacity and efficacy of medical therapy, and can guide cardiac rehabilitation after discharge. Patients who achieve at least 3 metabolic equivalents (METs) of the task have a good prognosis. Inability to achieve 3 METs, hypotension during exercise, or marked ST-segment depression or elevation is an indication for coronary angiography.
- 2. Stress imaging with echocardiography or radionuclide imaging is** recommended in patients who have uninterpretable electrocardiograms (e.g., baseline ST-T changes, LV hypertrophy, intraventricular conduction delays, paced rhythm, or digoxin-related effects). Addition of either imaging modality increases both the sensitivity and specificity of detecting CAD. Patients with

severe resting or exercise-induced LV dysfunction or evidence of extensive ischemia (large perfusion defect, multiple moderate perfusion defects, wall motion abnormalities at low-dose dobutamine or low heart rate, and stress-induced LV dilation) are considered high risk and should undergo coronary angiography.

3. **Dobutamine, adenosine, and dipyridamole** are pharmacologic agents used safely in conjunction with imaging for post-MI stress testing if a patient cannot exercise (see Chapter 6).

III. THERAPY AFTER MI

A. Coronary angiography

1. Indications

- a. Coronary angiography is indicated in patients with STEMI as well as in those with non-STEMI who are at high risk for clinical events, recurrent angina or ischemia on medical therapy, or high-risk findings on noninvasive stress testing.
 - b. An **“early invasive strategy” utilizing coronary angiography** is the preferred approach for patients at high risk for clinical events, including a high-risk score, elevated troponin, congestive heart failure, mechanical complications, and electrical or hemodynamic instability.
 - c. **Patients with a history of prior revascularization**, either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG), should generally be referred for angiography.
 - d. Coronary angiography to identify potential bypass targets is generally preferred prior to open heart surgery if a patient has surgical anatomy or has a mechanical complication post-MI requiring surgical intervention. Such complications of MI include ventricular septal rupture, LV aneurysm, and acute mitral regurgitation due to papillary muscle rupture. In rare instances when hemodynamic instability precludes angiography, the surgeon may bypass all or selected coronary arteries.
2. **Contraindications.** Catheterization should not be performed on patients who are ineligible for surgical or percutaneous revascularization because of severe comorbid conditions or who do not consent to angiography because of personal preference.
 3. **Controversy.** Low-risk, asymptomatic patients who have sustained an uncomplicated MI generally have a good long-term prognosis and may not need to undergo angiography. These patients presumably are those without high-risk features on noninvasive stress testing who will receive aggressive medical therapy and risk factor modification.
 4. **PCI.** A new era of PCI therapy that includes novel anticoagulants, antiplatelet agents, and newer generation drug-eluting stents continues to significantly enhance the options and outcomes for post-MI patients undergoing revascularization.

- B. **CABG after MI** can be divided into two categories: emergent and elective.

1. **Emergent CABG.** The indications and management considerations for emergent CABG are discussed in Chapter 1.
2. **Elective CABG.** CABG has been shown to provide a survival benefit for patients with left main (> 50% stenosis) or extensive three-vessel CAD. Surgical revascularization remains preferable for patients with severe LV dysfunction, diabetes, or two-vessel disease with proximal left anterior descending involvement and either high-risk noninvasive stress test results or LV dysfunction. However, the Arterial Revascularization Therapies Study (ARTS) demonstrated no significant difference in mortality, MI, or stroke among patients with multivessel disease and normal to moderately decreased LV function randomized to CABG versus PCI. The Synergy between Percutaneous Coronary Intervention with Taxus and

Cardiac Surgery (SYNTAX) trial evaluated PCI versus CABG for three-vessel or left main disease and nearly 30% of the patients had ACS. This trial demonstrated equivalent cumulative rates of major adverse cardiac or cerebrovascular events in the low (0 to 22) and intermediate (22–32) SYNTAX score patients, though there was a higher rate of adverse events in the high (≥ 33) SYNTAX score patients who underwent PCI. Target vessel revascularization was higher in the PCI group but stroke rate was higher in the CABG group.

3. **Operative risk.** No prospective, randomized trials have been performed to determine the optimal timing of elective CABG after MI. Most data suggest that CABG 3 to 7 days after MI is associated with a low operative mortality similar to that of elective bypass in patients without recent infarction. **Operative risk increases** among patients with LV dysfunction, advanced age, and multiple comorbid conditions (e.g., diabetes mellitus, chronic obstructive pulmonary disease, and chronic renal insufficiency). Emergent CABG and reoperations on patients with prior open heart surgery are associated with a higher operative mortality. If initiated previously, **clopidogrel** should be held for at least **5 days** prior to surgery and **prasugrel** for at least **7 days** prior to decrease perioperative bleeding risk. Ticagrelor is a reversible inhibitor of the adenosine diphosphate (ADP) receptor P2Y₁₂ that is more rapid acting and potent than clopidogrel. There was initial hope that the use of ticagrelor in patients with ACS undergoing urgent bypass surgery could reduce the time from cessation of antiplatelet agents to the time of surgery to just 2 or 3 days, given the more rapid reversal of platelet inhibition. However, results from the Study of Platelet Inhibition and Patient Outcomes (PLATO) demonstrated no difference in TIMI major bleeding or transfusion rates in patients with ACS who stopped clopidogrel 5 days prior to CABG compared with those who stopped ticagrelor 24 to 72 hours before surgery. Bleeding rates were equivalent even when surgery occurred 1 to 3 days after discontinuation of antiplatelets. Therefore, current ACC/AHA guidelines recommend **withholding ticagrelor for at least 5 days** prior to elective open heart surgery.

IV. SECONDARY PREVENTION

- A. **Smoking cessation is mandatory.** Smoking doubles the rate of reinfarction and death after MI, causes coronary artery spasm, and reduces the effectiveness of β -blocker therapy. The risk reduction attributed to smoking cessation is rapid and nearly equals that of post-MI patients who never smoked in only 3 years. Half of all patients who stop smoking after MI will begin smoking again within 6 to 12 months. Many approaches to smoking cessation have been attempted, including pharmacologic therapy, formal smoking cessation programs, hypnosis, and abstinence.
 1. **Nicotine substitutes** can be delivered by a variety of vehicles, including transdermal patches, chewing gum, nasal spray, and inhalers. These systems can deliver 30% to 60% of the nicotine of cigarettes. Although nicotine substitutes are not recommended for the acute phase of MI, use of these agents is safe in later phases. Patients who start smoking again should discontinue the use of nicotine substitutes.
 2. **Pharmacotherapy. Bupropion** appears to be an effective aid in smoking cessation. The dose is doubled after 3 days and it is then taken twice daily for 7 to 12 weeks. Patients set a goal to stop smoking 1 to 2 weeks into therapy. **Varenicline**, a partial agonist of nicotine receptors, provides nicotine stimulation while blocking cigarette nicotine effects. In a head-to-head trial, varenicline was more effective than bupropion at the 12-week time period, but data suggest no significant difference in rates of abstinence at 1 year. In addition, the FDA issued a communication in 2011 warning that varenicline may increase the risk of cardiovascular events.

3. **Recommendations.** Physicians can aid patients in their effort to stop smoking by using a stepped approach with education and a firm recommendation to quit smoking, devising a plan, and reinforcing the need to quit. Patients who are likely to relapse are older, less educated, or heavy smokers. Formal smoking cessation programs have been shown to have high rates of patient abstinence. Coinhabitants should also stop smoking to increase the likelihood of success.

B. Lipid management

1. **Low-density lipoprotein (LDL).** Most patients with acute MI have abnormal lipid profiles. Several large, secondary prevention trials have demonstrated that lowering of lipids can reduce the incidence of future mortality, reinfarction, and stroke.
 - a. **Diagnostic testing.** All patients who have had an MI should have a complete lipid panel (e.g., total cholesterol, LDL cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides (TG) determined during hospitalization).
 - b. **Diet.** Current ACC/AHA guidelines recommend that all patients should start the AHA step II diet (< 7% of total calories as saturated fat and < 200 mg/d cholesterol). However, adherence to step II diet is low.
 - c. **Therapy.** The National Cholesterol Education Program III (**NCEP III**) recommends a target LDL cholesterol level < 100 mg/dL, with a goal of < 70 mg/dL in very high risk patients (e.g., post-MI). Given the results of the Heart Protection Study (HPS), a 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, or **statin, should be initiated in all patients irrespective of LDL levels**, owing to potential benefits in addition to lipid lowering, including anti-inflammatory and antithrombotic effects. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) and Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) trials demonstrate that **early initiation of aggressive lipid-lowering statin therapy** during an ACS is associated with a **reduction in major cardiovascular events, including death**. Long-term compliance with statins is improved by in-hospital initiation of therapy (77% vs. 40%). Other therapies include bile acid sequestrants, niacin, gemfibrozil, moderate alcohol consumption (particularly red wine), and exercise. These may be used in conjunction with statin therapy.
2. **HDL.** Low HDL cholesterol level is an independent risk factor for MI. The NCEP III recommends an HDL level of at least 40 mg/dL. Consideration can be given to therapy with exercise, niacin, or gemfibrozil. An earlier trial, the Investigation of Lipid Level Management to Understand Its Impact in Atherosclerotic Events (ILLUMINATE), compared the use of a cholesteryl ester transfer protein (CETP) inhibitor torcetrapib plus statin versus statin alone and demonstrated increased HDL levels but significantly more adverse cardiovascular events and death from all causes in the torcetrapib group. A more recent trial with a newer drug anacetrapib, the Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib (DEFINE) study, has corroborated the beneficial effect on HDL and LDL but without an increase in cardiovascular side effects. Randomized clinical trials are currently evaluating the role of CETP inhibitors in event reduction.
3. **Triglycerides.** Hypertriglyceridemia may be an independent risk factor for CAD, commonly accompanied by low HDL levels or diabetes. Patients with TG levels above 200 mg/dL should be counseled to achieve non-HDL levels below 130 mg/dL. Fenofibrate or gemfibrozil can be added when TG levels exceed 200 mg/dL, particularly if a low HDL level is concurrent. Fibrates and high doses of statins can increase the risk of myopathy and should be avoided if possible. Omega-3 fatty acids may also be beneficial. Niacin can also be

considered for treatment of hypertriglyceridemia, but results from the recent Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial challenge the efficacy of extended-release niacin in preventing cardiovascular events. In this trial, even though extended-release niacin, when added to statin therapy, was able to decrease TG levels from 164 to 122 mg/dL, decrease LDL from 74 to 62 mg/dL, and raise HDL from 35 to 42 mg/dL, there was no difference in the primary end point (mean follow-up period of 3 years) consisting of a composite of cardiovascular outcomes.

- C. Diabetes management.** The American Diabetes Association recommends treating glucose levels with the goal of lowering the hemoglobin A1c to below or around 7% with the intent of decreasing micro- and macrovascular events. However, the concept of “intensive” glucose control has been challenged recently by trials demonstrating adverse events associated with this strategy in both the inpatient and outpatient settings. The Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial enrolled critically ill patients in an ICU setting and demonstrated increased mortality in the group randomly assigned to maintaining target glucose levels between 81 and 108 mg/dL versus a target glucose level of 180 mg/dL or less in the comparison group. Likewise, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, a large randomized study of over 10,000 outpatients, was discontinued due to excess mortality in the intensive therapy group assigned to achieve a hemoglobin A1c < 6% compared with the standard therapy group whose target A1c was between 7% and 7.9%.

D. Antiplatelet therapy

1. All patients who have had an MI should take **aspirin** upon presentation and continue indefinitely unless there are absolute contraindications. Aspirin therapy after MI results in a mortality reduction of 25 lives per 1,000 patients treated. Aspirin reduces the rates of vascular mortality, nonfatal stroke, and nonfatal MI. Doses of at least 75 to 162 mg daily are recommended for all patients presenting with ACS. Patients receiving dual antiplatelet therapy (e.g., aspirin plus thienopyridines) have fewer side effects, such as bleeding, at lower aspirin doses.
2. **Thienopyridines** (i.e., ticlopidine, clopidogrel, prasugrel, and ticagrelor) inhibit platelets via adenosine diphosphate antagonism. Clopidogrel is favored over ticlopidine because of a greater incidence of hematologic dyscrasia associated with ticlopidine. In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial, the combination of clopidogrel and aspirin was given early for ACS without ST-segment elevation, thereby reducing cardiovascular death, MI, stroke, in-hospital ischemia, and revascularization, with benefit seen at 1 year of therapy. The Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY) trial and Clopidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT) demonstrated the benefit of clopidogrel in patients with ST-elevation MI with reperfusion via lytics or PCI. Prasugrel is a more potent and more rapid inhibitor of ADP than clopidogrel, and the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel-TIMI (TRITON-TIMI) 38 trial demonstrated a reduction in the composite end point of death from all causes, nonfatal MI, or urgent target vessel revascularization with use of prasugrel compared with clopidogrel. Absolute contraindications to prasugrel use include prior stroke or transient ischemic attack. Patients with elevated risk of bleeding with prasugrel include those above age 75 years and those who weigh < 60 kg, and caution should be taken before prescribing this drug to these patients. Ticagrelor is the first reversible inhibitor of the P2Y₁₂ receptor and its action is more rapid and potent than that of clopidogrel. The PLATO trial demonstrated the superiority of ticagrelor over clopidogrel in reducing a composite of death from vascular causes, MI, or stroke in patients with ACS. It was also able

to demonstrate a greater reduction in the secondary end point of death from any cause using ticagrelor versus clopidogrel. Opinions vary as to whether to withhold thienopyridine loading prior to arrival in the catheterization lab in patients who are likely to require CABG because of an increased risk of bleeding and possible delay in surgery. If a patient requires urgent surgery, then clopidogrel and ticagrelor should be held for at least 24 hours to reduce the risk of major bleeding.

3. **Adding other medications**, such as sulfinpyrazone and dipyridamole, has not been shown to be more efficacious than aspirin alone and is not recommended for patients who have had an MI.

E. Warfarin sodium

1. **Patients** with a large anterior MI and LV thrombus treated with warfarin are at decreased risk for embolic stroke. Randomized trials do not exist, but many physicians recommend 6 weeks of warfarin therapy for this group of patients. This may assist in stabilization and endothelialization of the thrombus.
2. Data for the routine use of warfarin in conjunction with aspirin for secondary prevention of reinfarction are conflicting. The Combination Hemotherapy and Mortality Prevention (CHAMP) study and the Coumadin Aspirin Reinfarction Study (CARS) trial found no benefit from the addition of warfarin to standard aspirin therapy. However, combination therapy with aspirin and warfarin decreased infarct-related artery reocclusion and recurrent events in the Antithrombotics in the Prevention of Reocclusion in Coronary Thrombolysis (APRICOT 2) trial. The routine use of warfarin after MI is currently not recommended except for other established indications for anticoagulation, such as atrial fibrillation or prosthetic heart valves. Patients with concomitant use of dual antiplatelet agents for coronary disease are at significant risk for bleeding and hence this therapy should be used judiciously in these patients.

F. β -Blockers

1. **Indications.** β -Blockers are anti-ischemic, antihypertensive, and antiarrhythmic and they reduce LV wall stress. Mortality reduction results from decreased risk of sudden death, non-sudden cardiac death (SCD), and nonfatal infarction. Overall, the use of β -blockers reduces post-MI events by approximately 20%.
 - a. **The beneficial effects of β -blockers are greatest among patients who are at high risk**, such as patients with anterior infarction, complex ventricular ectopy, advanced age, and LV dysfunction. In the COMMIT trial, metoprolol given at presentation significantly reduced reinfarction and ventricular fibrillation in patients with acute MI who were hemodynamically stable; mortality benefit was not significant and this was probably the result of a net hazard during days 0 to 1 for patients presenting with New York Heart Association (NYHA) class III or IV heart failure. Several studies have found that only 50% of patients who sustain an MI actually receive β -blockers. **β -Blockers should be started as soon as possible in hemodynamically stable patients with MI** and should be continued indefinitely. Moderate LV dysfunction and compensated congested heart failure are not contraindications to β -blocker treatment.
 - b. **β -Blockers** without intrinsic sympathomimetic activity, such as carvedilol, metoprolol, propranolol, timolol, and atenolol, appear to have the greatest benefit. Reduction in heart rate seems to be important in achieving a mortality benefit.
2. **Contraindications.** Relative contraindications include second- or third-degree heart block, severe asthma, severe chronic obstructive pulmonary disease, severe or decompensated congestive heart failure, heart rate < 60 beats/min, hypotension with systolic blood pressure < 120 mm Hg, or other signs of a low-output state. In patients with heart rate > 100 beats/min, cardiogenic shock should be

ruled out by history and examination before administering β -blockers. Diabetes is not an absolute contraindication; however, the dose of the β -blocker may have to be reduced or discontinued if hypoglycemic episodes are frequent or severe.

G. Angiotensin-converting enzyme (ACE) inhibitors

1. **Indications.** Ventricular remodeling can be attenuated by ACE inhibitors, reducing ventricular dilation and development of congestive heart failure. During infarction, the expression of ACE increases within the myocardium. Several large randomized clinical trials have demonstrated that ACE inhibitors reduce mortality. These trials include Survival and Ventricular Enlargement (SAVE), Acute Infarction Ramipril Efficacy (AIRE), and Trandolapril Cardiac Evaluation (TRACE). The greatest benefit was found among patients with large areas of infarction, anterior infarction, and infarction that impaired LV function. **ACE inhibitor therapy should be considered in all patients after an acute MI** in the absence of contraindications. Therapy should be continued indefinitely in the setting of LV dysfunction (ejection fraction [EF] < 40%), heart failure, hypertension, or diabetes, although the ACC/AHA guidelines give class IIa recommendation for indefinite therapy in all patients after MI regardless of LV function or comorbidities. Angiotensin receptor blockers (ARBs) may be substituted if ACE inhibitors are not tolerated. The Valsartan in Acute Myocardial Infarction (VALIANT) trial evaluated post-MI patients with clinical signs of heart failure and low EF (< 35% by echo or angiography or < 40% by radionuclide ventriculography). Even though this study did not support superiority of valsartan therapy, it demonstrated noninferior mortality outcomes between groups treated with valsartan, captopril, or the two combined. However, adverse events including hypotension and medication dose reductions due to renal causes were more frequent in the valsartan and valsartan plus captopril groups. Cough, rash, and taste disturbances were more commonly reported in the captopril group.
2. **Side effects** include cough, worsening renal function, hypotension, and angioedema. Adverse events, especially renal impairment and hypotension, may be worse when ACE inhibitors and ARBs are used concomitantly, as was shown in the Ongoing Telmisartan Alone and in Combination with Ramipril Global End Point Trial (ON TARGET) and VALIANT trials.

H. Aldosterone antagonists

1. **Indications.** The Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS) trial demonstrated that eplerenone, when added to optimal medical therapy in post-MI patients with an EF of 40% or less, reduced the risk of death from any cause as well as the risk for a combination of death from cardiovascular causes and hospitalization for cardiovascular events. Optimal medical therapy included ACE inhibitors, ARBs, β -blockers, and coronary reperfusion.
 2. **Contraindications.** Because of its diuretic property and effect on the renin-angiotensin-aldosterone neurohormonal system, eplerenone should not be used in patients with renal dysfunction (creatinine > 2.5 mg/dL) or hyperkalemia (serum potassium > 5.0 mmol/L).
- I. **Calcium channel blockers.** The preferred agent after ACS is a β -blocker unless truly contraindicated. Calcium channel blockers are reserved for patients with **refractory angina** and not recommended for routine use after MI by the ACC/AHA guidelines. Longer acting preparations should be used if necessary, whereas short-acting dihydropyridine antagonists should be avoided.
1. **Indications.** The use of calcium channel blockers should be limited to patients with refractory angina or rapid atrial arrhythmias or to patients with clear contraindications to the use of β -blockers.
 2. **Contraindications.** Calcium channel blockers should be avoided in patients with congestive heart failure or high-degree atrioventricular block after an MI.

Short-acting dihydropyridine antagonists, such as nifedipine, may increase the risk of death or infarction after MI. Short-acting nifedipine may be especially harmful to patients with hypotension or tachycardia and can induce coronary steal or reflex sympathetic activation, which increases myocardial oxygen demand. Verapamil and diltiazem are contraindicated in the care of patients with LV dysfunction or congestive heart failure after MI. These agents may be useful in patients with contraindications to β -blockers who do not have LV dysfunction or congestive heart failure. Few data are available for the effect of the second-generation agents, amlodipine and felodipine, on survival after MI.

- J. **Estrogen replacement therapy.** The Heart and Estrogen/Progestin Replacement Study (HERS) found no benefit from hormone replacement therapy as secondary prevention for coronary disease, as the therapy was associated with an early increase in death and MI. The Women's Health Initiative (WHI) also observed an increased risk of cardiovascular events and breast cancer with hormone replacement therapy. Initiation of estrogen for primary and secondary prevention of cardiovascular disease is not recommended and should be discontinued at the time of MI.
- K. **Antioxidants.** Previous epidemiologic studies suggested that vitamin E, vitamin C, and β -carotene were associated with a lower incidence of CAD, but more recent studies failed to corroborate these findings. The HPS did not demonstrate a mortality or cardiovascular benefit from antioxidant therapy. Several other large randomized trials have failed to show either primary or secondary benefit for other similar vitamin supplementation strategies. The ACC/AHA guidelines, therefore, do not support the use of vitamin C or vitamin E, β -carotene, or folate with or without B₆ and B₁₂, for primary or secondary prevention.

V. PREVENTION OF SCD AFTER MI

A. Risk stratification for SCD

1. **All patients are at risk** for SCD after MI, with the greatest risk encountered during the first year (3% to 5%), most commonly due to ventricular arrhythmias.
2. **Reduced LV function (< 40%)** remains the best predictor of mortality. Measurement of LV function soon after MI may reflect myocardial stunning, so echocardiography should be re-measured again at the time of possible implantable cardioverter defibrillator (ICD) implantation, usually 40 days after MI for primary prevention or 3 months if reperfused after MI, via either PCI or CABG.
3. Many studies have found that patients who have more than six premature ventricular contractions per hour have a 60% relative increased risk for SCD. Patients with ventricular fibrillation or sustained ventricular tachycardia more than 48 hours after MI also are at increased risk. Monomorphic ventricular tachycardia is a manifestation of scar-related reentrant ventricular tachycardia.
4. Various techniques have been tested to identify patients at increased risk for SCD, but none is sensitive enough to be recommended for routine use. Signal-averaged ECG, heart rate variability, QT-interval dispersion, and baroreflex sensitivity are noninvasive tests, with each test having a low (< 30%) positive predictive value. Repolarization alternans (T-wave alternans) appears to have a higher sensitivity and specificity for inducible ventricular arrhythmia during electrophysiologic testing. Still invasive electrophysiologic testing has a low predictive value for future cardiac events. Consequently, **these modalities are not recommended for routine post-MI risk stratification.**

B. Therapy

1. The only medications proven to reduce risk for SCD are **β -blockers**. All patients should receive β -blockers after an MI unless absolutely contraindicated.
2. **Other medications.** Amiodarone has multiple antiarrhythmic effects, but is primarily classified as a class III agent. Trials of amiodarone in the care of

patients who have had an MI with LVEF < 40% have shown conflicting results, although a significant reduction in mortality has not been demonstrated. Amiodarone is still the preferred antiarrhythmic therapy for symptomatic or sustained ventricular arrhythmias in post-MI patients. Lidocaine is sometimes used as an alternative to amiodarone, but it should not be administered without documented ventricular tachycardia. Likewise, the prophylactic use of sotalol after MI has been associated with increased mortality. The use of type IC antiarrhythmic agents (i.e., encainide, flecainide, and propafenone) after MI is contraindicated.

3. **Implantable cardioverter-defibrillator. Early implantation of an ICD after MI has not been shown to be beneficial.** The Defibrillator IN Acute Myocardial Infarction Trial (DINAMIT) found no mortality benefit despite a reduction in arrhythmogenic death when ICDs were implanted within 40 days after MI despite LVEF < 35%. The Immediate Risk-Stratification Improves Survival (IRIS) trial enrolled patients at increased risk for sudden death within 31 days of an MI. Such patients were those with an EF = 40% and a heart rate > 90 beats/min or those with evidence of nonsustained ventricular tachycardia on ECG or holter monitor, or both. Overall mortality was not reduced in those in whom an ICD was implanted compared with the group treated with medical therapy. On the contrary, the Multicenter Automatic Defibrillator Implantation Trial II (MADIT II) investigators and others demonstrated a survival benefit in patients with LV dysfunction and previous MI receiving a prophylactic ICD (see Chapter 23). The Multicenter Unsustained Tachycardia (MUST) trial noted improved survival with ICD implantation in patients who had inducible ventricular arrhythmias with electrophysiologic (EP) study. Therefore, class I indications for ICD therapy post-MI include patients with ischemic cardiomyopathy EF < 35% with NYHA class II or III symptoms at least 40 days post-MI, ischemic cardiomyopathy EF < 30% with NYHA class I symptoms at least 40 days post-MI, and ischemic cardiomyopathy EF < 40% with inducible ventricular fibrillation or sustained ventricular tachycardia on EP study. Patients who undergo either percutaneous or surgical revascularization after MI should have an assessment of LV function after 3 months to help determine the appropriateness of ICD implantation.

VI. THERAPY AND PREVENTION AFTER HOSPITAL TREATMENT

- A. **Cardiac rehabilitation programs** seek to improve the biopsychosocial aspects of patients after MI by addressing the benefits of exercise, weight loss, proper diet, smoking cessation, and good mental health. Both randomized data and meta-analyses have demonstrated a mortality benefit associated with cardiac rehab in patients after MI.
 1. Formal rehabilitation programs use **exercise and patient education** to help patients modify their lifestyles. The benefits of cardiac rehabilitation include improvement in a patient's commitment to treatment, increased functional capacity, and reduced likelihood of readmission for recurrent ischemia. The **social support** offered is associated with a 25% reduction in both cardiac and all-cause mortality. Depression after MI is common, and patients must be screened during follow-up. Depression is also an independent risk factor for mortality, possibly by decreasing commitment to therapy and exercise. There are limited data regarding the safety and efficacy of antidepressant medications in the post-MI setting. In a small study, sertraline was found to be safe and efficacious for the treatment of major depressive disorder after ACS.
 2. **Home programs and family care.** Although cardiac rehabilitation has been shown to have many benefits, less than one-half of patients who have had an MI participate in formal programs. Home programs may be helpful, but they do not provide the social network found in group rehabilitation programs. Because most cardiac arrests after MI occur within 18 months after discharge, family members should be encouraged to learn basic cardiopulmonary resuscitation.

- B. Soon after receiving the diagnosis of MI, patients should be counseled regarding **lifestyle modification** to improve weight control, diet, exercise, lipid control, blood pressure, and smoking cessation.
 1. Optimal control of hypertension and diabetes should be achieved. The Diabetes Control and Complication Trial (DCCT) and the United Kingdom Prospective Diabetes Study (UKPDS) determined the need for strict glucose control of insulin and non-insulin-dependent diabetes. Improvement in serum glucose levels decreases the progression of microvascular complications. In both trials, a trend toward decreased microvascular events among the groups that received aggressive treatment was observed.
 2. **Weight reduction.** Among adults in the United States, approximately two-thirds of the population, or nearly 130 million persons, are overweight (i.e., body mass index > 25 kg/m²). Patients should be encouraged to achieve (or maintain) an ideal body weight. All patients should begin an AHA step II diet to achieve lipid goals. Fewer than 50% of patients comply with step II diet, and many patients will need additional pharmacologic therapy to manage hyperlipidemia.
 3. **Resumption of daily activities**
 - a. At discharge, all patients who have had an MI should receive information regarding resumption of sexual activity, driving, work, and exercise.
 - b. **Sexual activity** can be resumed within a week for most patients. Oral phosphodiesterase inhibitors **are absolutely contraindicated in patients on concomitant nitrate therapy. Nitrates should not be used** within 24 hours of sildenafil and 48 hours of tadalafil. Vardenafil has a similar half-life as sildenafil and thus similar precautions should be taken. **Driving** can also be resumed within a week. Most patients who have had an MI who do not have symptoms can **return to work** within 2 weeks.
 - c. A patient's performance on an **exercise test** can be used to generate an activity prescription. Patients who can perform at least 5 METs on a submaximal exercise test without marked ST-segment depression or development of angina have a good long-term prognosis.
 - d. Because of the lowered oxygen tension in most commercial aircraft (pressurized to 7,500 to 8,000 feet), only patients in stable condition should **travel by plane** within the first 2 weeks after MI. They should carry sublingual nitroglycerin and request a wheelchair for transportation.

ACKNOWLEDGMENTS: *The authors thank Drs. Shaun Senter, Mehdi Shishehbor, John H. Chiu, and Elaine K. Moen for their contributions to earlier editions of this chapter.*

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CHAPTER

6

Amar Krishnaswamy
Samir R. Kapadia

Stable Angina

- I. **INTRODUCTION.** Angina pectoris, derived from the Greek “ankhon” (strangling) and the Latin “pectus” (chest), is the term used to describe the syndrome of chest discomfort resulting from myocardial ischemia. Angina is characterized as stable or unstable on the basis of symptom pattern.
 - A. Anginal symptoms are defined as stable if there is no substantial change in symptoms over several weeks. Symptoms of stable angina can fluctuate from time to time, depending on myocardial oxygen consumption, emotional stress, or change in ambient temperature. In general, the clinical definition of stable angina pectoris closely correlates with the stability or quiescence of an atherosclerotic plaque and decreased clinical risk.
 - B. Angina is said to be unstable when the symptom pattern worsens abruptly (increase in frequency and duration) without an obvious cause of increased myocardial oxygen consumption. Similarly, the onset of rest angina in a patient for whom angina was previously provoked by some degree of exertion may signal an unstable syndrome.
 - C. For some patients with new-onset angina that has been stable over a few weeks, clear distinction between stable and unstable angina is not possible. These patients can be considered to be in an intermediate stage between unstable and stable angina.

II. CLINICAL PRESENTATION. For most patients with chest pain, the diagnosis of angina pectoris can be made with careful history taking. The presence of risk factors for coronary artery disease (CAD), such as hypertension, diabetes mellitus, smoking, family history, hyperlipidemia, claudication, and advanced age, increases the likelihood that the chest pain is being caused by myocardial ischemia.

A. Signs and symptoms. The constellation of symptoms characteristic of angina pectoris includes the following four cardinal features.

1. **Location.** Discomfort is commonly located in the retrosternal area with radiation to the neck, shoulders, arms, jaws, epigastrium, or back. In some instances, it involves these areas without affecting the retrosternal area.
2. **Relation to a trigger.** Symptoms are typically triggered by physical activity, emotional stress, exposure to cold, consumption of a heavy meal, or smoking.
 - a. Some patients will experience the resolution of angina despite continued exertion, which is known as the walk-through phenomenon. Others may experience the warm-up phenomenon, in which an initial exertion produces angina but a similar second exertion does not reproduce anginal symptoms. These circumstances probably result from the recruitment of collateral coronary flow during the initial episode of ischemia.
 - b. Decubitus angina, which is a less common manifestation, occurs with a change in posture and is believed to be caused by a shift in blood volume. Nocturnal angina, which occurs at night, is frequently associated with nightmares and tachyarrhythmias.
3. **Character.** Most patients describe angina as a vague chest discomfort. They describe it as a squeezing, burning, tight, choking, heavy, and occasionally hot or cold sensation. Many patients do not perceive angina as pain per se. Some patients may experience dyspnea, profound fatigue, weakness, lightheadedness, nausea, diaphoresis, altered mental status, or syncope in the absence of any chest discomfort. These symptoms are often referred to as anginal equivalents. Non-cardiac causes of chest pain (gastrointestinal, respiratory, musculoskeletal, etc.) may be indicated by fleeting chest pain, unrelenting chest pain not affected by activity, antecedent chest trauma, association with food intake, location inferior to the umbilicus, pleurisy, etc.
4. **Duration.** The chest pain associated with ischemia typically lasts 3 to 5 minutes. Ischemic pain usually does not last more than 30 minutes without causing myocardial infarction (MI). Chest pain triggered by emotional distress tends to last longer than that triggered by exercise. Chest pain that lasts < 1 minute is unlikely to be of cardiac origin, especially when it is not associated with other typical symptoms or findings.
5. It should be stressed that women may present with symptom constellations that may be atypical in location or quality in comparison to the symptoms described by men or manifest as anginal equivalents such as nausea or dyspnea.
6. Chest pain is defined as “typical angina” if it consists of characteristic substernal discomfort, is provoked by stress, and is relieved by rest or nitroglycerin. It is considered “atypical” if it involves two or less of the previously mentioned criteria.
7. **Classification.** Various classifications are available to assess the severity and to predict the outcome among patients with angina. The Canadian Cardiovascular Society classification is the most popular one (Table 6.1). Other classification systems include the Specific Activity Scale, the Duke Activity Status Index, and the Braunwald classification.

B. Physical findings. For patients with a history of chest pain, physical examination helps identify risk factors for CAD and occult cardiac abnormalities.

1. **The signs associated with a high risk for CAD** include elevated blood pressure or manifestations of hypertensive vascular disease such as retinal arteriopathy, signs of hyperlipidemic conditions including corneal arcus or xanthelasma, and evidence of carotid or other peripheral vascular disease.

TABLE 6.1 Classification of Angina

CCS class	Definition	Comment
I	Ordinary physical activity does not cause angina	Angina only with extraordinary exertion at work or recreation
II	Slight limitation of ordinary activity	Angina with walking more than two blocks on a level surface or climbing more than one flight of stairs at a normal pace
III	Marked limitation of ordinary physical activity	Walking one to two blocks on a level surface or climbing one flight of stairs at a normal pace
IV	Inability to carry on any activity without discomfort	Angina at rest or with minimal activity or stress

CCS, Canadian Cardiovascular Society.

2. **Physical examination** performed during an episode of chest pain may reveal rales, an S_3 or S_4 gallop, or a systolic murmur from ischemic mitral regurgitation, all of which generally disappear with resolution of symptoms.

C. Baseline electrocardiogram (ECG)

1. A baseline ECG is **useful for the initial screening** of CAD, although about 60% of patients with chest pain have a normal ECG. Presence of a Q wave or persistent ST depression is associated with an unfavorable outcome. The ECG can also demonstrate other abnormalities, such as left ventricular (LV) hypertrophy, bundle branch block, and preexcitation syndromes.
2. Information obtained from the ECG is **useful in the assessment of chest pain** and helps to stratify patients who are at risk for an adverse event.
3. ECG at the time of chest pain can also **help identify the cause of the chest pain**. Transient changes in the T-wave, ST-segment, or conduction patterns point toward a cardiac source of the chest pain. A normal ECG does not exclude ischemia as being the etiology of chest pain.

III. DIAGNOSTIC TESTING. For a patient with stable CAD, investigations are aimed at risk stratification and management of symptoms and unfavorable outcomes.

- A. **Stress testing.** The basic principle of stress testing is to provoke ischemia or produce coronary vasodilation, followed by functional assessment with different systems to detect ischemia. Stress tests can be categorized according to the methods used to provoke and detect myocardial ischemia. The sensitivity and specificity of each test to identify coronary stenosis vary according to the study population, definition of disease, definition of a positive test result, protocol used for the stress testing, and experience of the interpreter. The following is a brief overview of noninvasive cardiac testing. **For a thorough discussion on noninvasive imaging and stress modalities, please refer to the specific chapters.**

1. **Methods to induce ischemia.** Exercise is the most physiologically sound and useful method for inducing ischemia. An exercise test is considered adequate if 85% or more of age-predicted maximum heart rate ($220 - \text{age}$) is achieved. Exercise testing provides an objective assessment of functional capacity, which provides useful prognostic information. Pharmacologic testing, with dobutamine or adenosine/adenosine derivatives (i.e., dipyridamole), can be used for patients who cannot exercise adequately.

2. Methods to assess ischemia

- a. **Stress ECG.** Exercise ECG provides useful diagnostic information about the patients with normal baseline ECGs who are at intermediate risk for CAD. Stress ECG is also used to create an exercise prescription in patients with stable angina. The sensitivity and specificity of stress ECG are poor among patients with an abnormal baseline ECG, LV hypertrophy, ventricular pacing, left bundle branch block (LBBB), or intraventricular conduction disturbance and among patients taking digitalis or other medications that affect conduction and depolarization. Electrocardiographic changes during dipyridamole or adenosine infusion have high specificity but poor sensitivity. Electrocardiographic changes during dobutamine infusion have sensitivity and specificity similar to those of exercise ECG.
 - b. **Echocardiographic imaging.** Stress echocardiography is an economical test with good specificity for identifying the location and extent of ischemic territories. This is assessed by the induction of regional wall motion abnormalities with stress or dilation of the left LV cavity with stress (which may indicate global ischemia). If the patient is unable to exercise, a dobutamine stress test can be performed. A biphasic response with dobutamine, in which contractility initially increases with lower doses of dobutamine and then decreases with higher doses, is diagnostic of ischemia. Augmentation of contractility in hypokinetic segments may indicate the presence of hibernating myocardium in a specific coronary distribution. At some medical centers, dipyridamole and adenosine stress tests are performed with echocardiographic imaging. This method is less sensitive in detecting underlying CAD. Results of stress echocardiography are difficult to interpret in some patients with a hypertensive response to exercise and in some patients with severe mitral or aortic regurgitation. Preexisting wall motion abnormalities may further complicate image interpretation.
 - c. **Radionuclide imaging.** Single-positron emission computed tomography (SPECT) can be performed after injection with thallium 201 or technetium (Tc) 99m-labeled radiopharmaceuticals. Positron emission tomography (PET) can be performed utilizing rubidium 82 or ¹³N ammonia tracers. PET imaging provides greater spatial resolution and diagnostic accuracy in comparison with SPECT imaging. Injection of fluorine 18-labeled deoxyglucose (FDG) allows assessment of myocardial viability in patients with resting perfusion defects. The sensitivity and specificity of nuclear testing are decreased among patients with severe obesity, balanced three-vessel disease, and LBBB.
- B. Echocardiography** provides useful information in the overall assessment of suspected stable angina.
1. Regional wall motion abnormalities involving the left ventricle are commonly caused by CAD and may represent resting ischemia or prior MI. Any impairment in LV systolic function, LV hypertrophy, and presence of substantial mitral regurgitation are associated with heightened clinical risk and poor outcome. LV systolic function may guide the choice of medical therapy versus revascularization.
 2. Echocardiography is the test of choice to quantify aortic stenosis or the presence of hypertrophic cardiomyopathy.
- C. Magnetic resonance imaging (MRI)**
1. Ischemic evaluation using pharmacologic stress (dobutamine or adenosine) and cardiovascular magnetic resonance can also be utilized to evaluate myocardium in jeopardy. MRI uses gadolinium as a contrast medium to evaluate regional wall motion abnormalities and ejection fraction, as well as segmental myocardial perfusion (when using adenosine). MRI can also provide direct visualization of the

coronary arteries, although computed tomography (CT) angiography is much better for this application.

2. Delayed-phase gadolinium imaging also provides information on the location and transmural of myocardial scar.
3. The weaknesses include increased cost, lack of portability, and unsuitability for use in the growing population of patients with pacemakers and defibrillators.

D. Electron beam computed tomography (EBCT)

1. EBCT is a noninvasive method of obtaining cross-sectional images of the heart and allows quantification of coronary artery calcification. The test is rapid and provides a “calcium score.” This test does not provide sufficient detail to accurately quantify and grade stenosis due to atherosclerotic lesions. An increasing calcium score correlates strongly with heightened risk of cardiovascular events and abnormal findings should lead to further risk factor modification and cardiovascular risk assessment.

E. Multidetector computed tomography

1. **Strengths.** Coronary computed tomography angiography (CCTA) allows for the evaluation of the epicardial coronary tree using a noninvasive approach. The sensitivity of CCTA for assessing coronary stenosis approaches 97% with a specificity of 86% when using a 64-slice technology. With technologic advances allowing a greater number of slices to be acquired in current practice, the accuracy of this study is expected to increase. Importantly, the negative predictive value of CCTA is 99%, with an optimal study and appropriate patient selection. Severe coronary artery calcification or previous coronary stent placement may significantly detract from image quality, rendering the evaluation of specific coronary segments uninterpretable. Larger stents may be grossly evaluated for patency but accurate quantification for in-stent restenosis in anatomical locations distal to the left main coronary artery (LMCA) is not always feasible.

F. Coronary angiography

1. **Strengths.** Coronary angiography is the standard for anatomic assessment of coronary arterial stenosis and provides important prognostic information.
 - a. Patients with > 75% stenosis involving at least one coronary artery have a lower survival rate than patients with 25% to 50% or < 25% stenosis. Even for mild stenosis, risk for MI is markedly higher than for no stenosis.
 - b. The severity of lesions demonstrated with angiography is not predictive of plaque stability; two-thirds of patients with acute MI have stenosis of > 50% diameter at the site of plaque rupture before MI. It is possible, however, to assess plaque instability on the basis of angiographic characteristics or morphologic features of the lesion.
 - (1) Eccentric lesions with narrow necks, overhanging edges, or scalloped borders (type II plaques) are more unstable than concentric lesions with smooth borders (type I plaques).
 - (2) Lesion roughness (i.e., irregular borders) is predictive of plaque instability and heightens the risk of future infarction.
 - (3) The morphologic characteristics of the plaque help in judging the feasibility and risk of percutaneous or surgical intervention.
 - c. Ventriculography performed at the time of selective coronary angiography adds an important dimension to risk stratification by providing an index of LV systolic function and regional wall motion characteristics as well as the presence and degree of mitral regurgitation.
2. **Indications.** In the management of stable angina, use of angiography is variable. An American College of Cardiology and American Heart Association (ACC/AHA) task force classified the indications for coronary angiography into three categories. The relevant indications in the context of stable angina are presented in Table 6.2.

TABLE 6.2 **Indications for Coronary Angiography in Stable Angina**

Class I (general agreement among cardiologists)
Severe anginal symptoms (CCS class III or IV) with optimal medical therapy
Stress testing indicators of high-risk coronary disease
Survivors of sudden cardiac arrest
Symptoms of congestive heart failure with angina
Clinical predictors of severe CAD
Class II (frequently used but controversial)
Symptoms of angina and positive stress test
Inadequate information from noninvasive testing
Severe angina that improves to mild/moderate angina with medical therapy
Anginal symptoms and intolerance of medical therapy
Asymptomatic patients with positive stress test
Patients who are unable to be evaluated noninvasively
Patients with an occupation that involves an unusual degree of risk
Patients suspected of ischemic symptoms caused by nonatherosclerotic coronary disease (i.e., vasculitis and radiation coronary disease)
Suspicion of coronary vasospasm with the need for provocative testing
Suspicion of left main or three-vessel coronary disease
Recurrent hospitalization for chest pain and need for definitive coronary evaluation
Patients with intermediate or high probability of CAD and a desire for definitive diagnosis
Class III (unjustified use of angiography)
Mild symptoms that resolve with medical therapy
Patients who would not undergo revascularization
Patients with low probability of CAD and a desire for definitive diagnosis

CAD, coronary artery disease; CCS, Canadian Cardiovascular Society.

3. **Limitations.** Coronary angiography underestimates plaque burden, possibly because of vascular remodeling and the diffuse nature of the disease. Coronary angiography does not depict intraluminal plaque burden and does not show coronary flow reserve. Adjunctive use of intravascular ultrasonography (IVUS) greatly facilitates the investigation of hazy areas on coronary angiograms, which may be caused by calcium, thrombus, severe eccentric lesion, or dissection. The IVUS can also assess positive and negative remodeling, which has been shown to correlate with stable and unstable syndromes.
- G. **Intravascular ultrasonography** allows visualization of the cross-sectional image of coronary arteries. This modality helps to quantitate plaque area, artery size, and luminal stenosis; assess hazy areas on coronary angiograms, questionable areas of stenosis, and extent of stenosis; and sometimes determine the calcium content of a plaque. Hypodense areas in a plaque may correlate with high lipid content, which may indicate fast-growing or potentially unstable plaque. This information can help

assess the need for and options of therapy. This modality does not, however, have a role in routine evaluation of patients with stable angina, due to the invasive nature of the test.

- H. **Optical coherence tomography (OCT)** is a relatively new intracoronary imaging modality that has better resolution than IVUS but provides less depth. It has been used, thus far, almost exclusively as a research tool, but a number of studies are currently ongoing to establish its clinical utility. Potential contributions of OCT include characterization of plaque, better understanding of stent characteristics (degree of apposition and stent endothelialization, etc.), and arterial remodeling. This technique requires injection of contrast medium during imaging (usually totaling 12 to 20 cc per run) and so may be of limited use in patients with chronic kidney disease.
- I. **Invasive functional assessment.** Invasive assessment of the functional significance of an intermediate stenosis can be made by means of coronary blood flow measurement with intracoronary Doppler ultrasound and direct measurement of a pressure gradient across a stenosis.
 1. With the help of a small transducer mounted on a guidewire, coronary blood flow can be measured by means of a fixed sample volume and pulsed Doppler.
 - a. In the left coronary artery, most coronary flow occurs during diastole. In normal arteries, a ratio of proximal-to-distal flow velocity approaching 1 is considered normal. In the presence of coronary stenosis, coronary blood flow becomes mainly systolic because the diastolic component of the flow is jeopardized first.
 - b. Three indices can help identify physiologically important stenoses:
 - (1) Diastolic-to-systolic average peak coronary flow velocity ratio of < 1.8 distal to the obstruction
 - (2) A proximal-to-distal average peak coronary flow velocity ratio of > 1.7
 - (3) Coronary flow reserve (i.e., increase in coronary flow with adenosine, which is administered after intracoronary nitroglycerin) with a less than twofold increase in peak velocity
 2. **Direct measurement of pressure gradients** can be accomplished with a transducer mounted on a catheter. Ratio of mean pressure distal and proximal to the lesion after maximum vasodilation (fraction flow reserve or FFR) of < 0.75 to 0.80 indicates a hemodynamically significant lesion. These techniques supplement angiography in determining the functional significance of an intermediate (30% to 70%) angiographic stenosis. In a group of patients with angiographically intermediate stenosis, the Fractional Flow Reserve versus Angiography for Multivessel Evaluation (FAME) investigators were able to demonstrate lower rates of mortality and MI (8.4% vs. 23.9%, $p = 0.02$) with less stent placement when a strategy of FFR-guided (vs. angiography-guided alone) percutaneous coronary intervention (PCI) was pursued.
- J. **Holter monitoring**
 1. After MI, increased ventricular ectopy is predictive of increased cardiovascular morbidity and mortality. This association is less important among patients with stable angina without prior MI, and routine Holter testing for risk stratification is not indicated. No medical treatment aimed at suppressing ventricular ectopy has been shown to improve outcome.

IV. THERAPY. The goals of therapy are to prevent cardiovascular morbidity and mortality and to improve quality of life.

- A. **Therapeutic options.** Medical therapy, PCI, and coronary artery bypass grafting (CABG) have all been shown to control symptoms and improve exercise time to ischemia. In an era of rudimentary medical therapy, CABG has been proven to decrease cardiovascular mortality in specific patient subsets. Although PCI has been shown to improve stable anginal symptoms and improve quality of life, a decrease in mortality has not been proven in randomized controlled trials (RCTs).

B. Pharmacologic therapy

1. Platelet inhibitors

- a. The Antiplatelet Trialists' Collaboration was a meta-analysis that included approximately 100,000 patients from 174 trials involving antiplatelet therapy. This data set showed that aspirin (acetylsalicylic acid, ASA) reduced the rate of stroke, MI, and death among high-risk patients, including those with stable angina without previous MI. A recent systematic review confirms that, while optimal dosing is controversial, there is general support in the literature for limiting the dose of ASA to 75 to 81 mg daily. Approximately 5% to 10% of patients with CAD have aspirin resistance, defined as a lack of decrease in platelet function associated with aspirin use. Aspirin resistance has been shown to result in higher thrombotic events in people with peripheral vascular disease. Patients who demonstrate increased platelet reactivity despite aspirin therapy have increased risks for stroke, MI, and vascular death compared with aspirin responders.
- b. Among patients with true allergy or intolerance to aspirin, clopidogrel has been shown to decrease the frequency of fatal and nonfatal vascular events in peripheral, cerebral, and coronary vessel diseases.
 - (1) Clopidogrel is a second-line therapy in patients unable to tolerate aspirin. In high-risk patients with prior cardiac surgery or ischemic events, the use of clopidogrel as monotherapy, or in addition to aspirin, is beneficial. In patients receiving bare-metal stenting (BMS) for stable coronary disease, at least 1 month of dual antiplatelet therapy (DAPT; aspirin 81 mg plus clopidogrel 75 mg daily) is recommended. The use and duration of DAPT with clopidogrel and aspirin in the setting of drug-eluting stent (DES) implantation are currently under intense review, with concerns of very late stent thrombosis (ST) on one hand and studies questioning the benefit of extended duration DAPT on the other. The most recent ACC/AHA PCI guidelines recommend 12 months of DAPT in patients undergoing DES, though longer duration may be considered (class IIb) in specific high-risk patient/stent subsets. Clopidogrel is usually well tolerated and has few side effects.
 - (2) In the initial analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial, performed on a large group of patients included with either prior cardiovascular events or multiple cardiovascular risk factors, there was no benefit from the use of DAPT over aspirin alone in preventing MI or death. A prespecified analysis of higher risk patients only (such as those with prior MI) did show a decrease in cardiovascular events for the group receiving clopidogrel in addition to aspirin. This suggests that an appropriate group of patients may benefit from prolonged DAPT.
2. **Lipid-lowering agents.** Among patients with established CAD, secondary prevention with lipid-lowering therapy, specifically statins, has demonstrated marked reduction in risk for subsequent cardiovascular events. Statins are potent inhibitors of 3-hydroxy-3-methylglutaryl coenzyme reductase (HMG-CoA reductase). They are the most effective medical therapy for lowering levels of low-density lipoprotein (LDL) and have also been shown to upregulate nitric oxide (NO) synthase, decrease expression of endothelin-1 mRNA, improve platelet function, and decrease production of detrimental free radicals; all of these promote normal endothelial function.
 - a. **Indications.** The Scandinavian Simvastatin Survival Study (4S), Cholesterol and Recurrent Events (CARE), Long-term Intervention with Pravastatin in Ischemic Disease (LIPID), and Heart Protection Study (HPS) trials have provided convincing evidence that in patients with evidence of cardiovascular

disease with normal or elevated cholesterol levels, statins decrease mortality, the rate of MI and stroke, and the need for CABG.

- b. **Effectiveness.** Recent studies have shown that in patients with stable CAD (treating to new targets [TNT]) or post-acute coronary syndrome (ACS) (PROVE IT-TIMI-22), aggressive lipid lowering to an LDL goal of 70 mg/dL decreases the risks of cardiovascular death, MI, and stroke compared with patients treated to an LDL goal of 100 mg/dL. There is also a suggestion that aggressive statin therapy retards and even results in a mild degree of plaque regression as measured by IVUS.
 - c. **Choice of agents.** Statins should be the first line of therapy in patients with CAD. The quantification of lipoprotein(a) [Lp(a)], fibrinogen, apolipoprotein (apo A), and apolipoprotein B₁₀₀ (apo B₁₀₀) is investigational. Bile acid sequestrants primarily reduce LDL cholesterol and should not be used in patients with triglyceride levels higher than 300 mg/dL, because these agents may exacerbate hypertriglyceridemia. Nicotinic acid reduces LDL and triglyceride levels and is the most effective of the available lipid-lowering medications at increasing high-density lipoprotein (HDL) level. It is also the only agent that lowers Lp(a). Fibric acid derivatives are most effective against hypertriglyceridemia; they raise HDL level modestly and have little effect on LDL. They are the first line of treatment in patients with triglyceride levels higher than 400 mg/dL. ω -3 Fatty acids may also be used to treat hypertriglyceridemia that is refractory to niacin and fibric acid therapy. Agents to raise HDL cholesterol, cholesteryl ester transfer protein inhibitors, are currently undergoing intensive clinical evaluation in RCTs and may provide a beneficial treatment adjunct to statin therapy in the future.
 - (1) Current evidence supports aggressive lowering of LDL cholesterol levels in patients with established coronary disease, or CAD equivalents, to a goal of 70 mg/dL (class IIa). A level of HDL cholesterol > 45 mg/dL and triglycerides < 150 mg/dL are secondary goals of dietary, lifestyle, and pharmacologic therapies.
 - (2) The side effects of statin therapy, including myositis and hepatitis, are quite rare. The package inserts recommend liver function test evaluation prior to initiation of therapy (or increase in dose) and 3 months thereafter. Blood tests are not necessary for routine follow-up of patients who are stable on these medications and should only be measured based upon clinical suspicion of an untoward effect.
3. **Nitrates** (Table 6.3)
- a. **Mechanism of action.** Nitrates decrease cardiac workload and oxygen demand by means of reducing preload and afterload of the left ventricle. They also redistribute blood flow to the ischemic subendocardium by means of decreasing LV end-diastolic pressure, vasodilation of epicardial vessels, and improvement of collateral blood flow to ischemic tissue. In an adjuvant role, nitrates may also be weak inhibitors of platelet aggregation.
 - b. **Evidence for effectiveness.** Nitrates can decrease exercise-induced myocardial ischemia, alleviate symptoms, and increase exercise tolerance in patients with stable angina.
 - (1) Adding nitrates to an optimal β -blocker regimen does not improve frequency of anginal episodes, glyceryl trinitrate consumption, exercise duration, or duration of silent ischemia.
 - (2) In some small studies, the efficacy of nitrates in reducing anginal episodes was increased with concomitant use of angiotensin-converting enzyme (ACE) inhibitors.
 - (3) No study has shown survival benefit with the use of nitrates to treat patients with chronic stable angina.

TABLE 6.3 **Nitrates**

Medication	Route of administration	Each dose	Frequency
Nitroglycerin (glyceryl trinitrate, Nitro-Bid, Nitrostat, and Nitro-Dur)	Sublingual tablet	0.15–0.6 mg	As needed
	Sublingual spray	0.4 mg	As needed
	Sustained-release capsule	2.5–9.0 mg	Every 6–12 h
	Ointment (topical)	0.5–2" (1.25–5 cm)	Every 4–8 h
	Disk (patch)	1 disk (2.5–15 mg)	Every 24 h
	Intravenous	5–400 µg/min	Continuous
	Buccal tablet	1 mg	Every 3–5 h
Isosorbide dinitrate (Isordil, Sorbitrate, and Dilatrate SR)	Sublingual tablet	2.5–10 mg	Every 2–3 h
	Chewable tablet	5–10 mg	Every 2–3 h
	Oral tablet	10–40 mg	Every 6 h
	Sustained-release tablet	40–80 mg	Every 8–12 h
Isosorbide-5-mononitrate (Imdur and Ismo)	Sublingual tablet	10–40 mg	Every 12 h
	Sustained release	60 mg	Every 24 h
Erythryl tetranitrate (Cardilate)	Sublingual tablet	5–10 mg	As needed
	Tablet	10 mg	Every 8 h

- c. **Selection of preparations.** Because nitrates have a fast onset of action, a sublingual tablet or oral spray offers immediate relief of an anginal episode.
 - (1) For short-term prophylaxis (up to 30 minutes), nitroglycerin tablets can be used when activities known to precipitate angina are anticipated. Timing and frequency of the doses can be individualized according to the diurnal rhythm of anginal episodes. A nitrate-free interval of about 8 hours is adequate for preventing tolerance.
 - (2) Use of long-acting medications and transcutaneous delivery systems improves compliance but still necessitates a nitrate-free interval.
- d. **Side effects.** Oral nitrates should be taken with meals to prevent heartburn.
 - (1) Headache is common and can be severe. Severity usually decreases with continued use and often can be controlled by decreasing the dose.
 - (2) Transient episodes of flushing, dizziness, weakness, and postural hypotension can occur, but these effects are usually abrogated by positioning and by other procedures that facilitate venous return.
- e. **Drug interactions**
 - (1) Hypotension can occur with the use of other vasodilators, such as ACE inhibitors, hydralazine, or calcium channel blockers. **Concurrent use of PDE5 inhibitors like sildenafil (Viagra) and nitrates can lead to severe hypotension and, therefore, is absolutely contraindicated.**
- f. **Controversies**
 - (1) **Tolerance.** Sustained therapy attenuates the vascular and antiplatelet effects of nitrates. Although the basis for this phenomenon of nitrate tolerance is not completely understood, sulfhydryl depletion, neurohormonal activation, and increased plasma volume are likely involved.

Administration of *N*-acetylcysteine, ACE inhibitors, or diuretics does not consistently prevent nitrate tolerance. Intermittent nitrate therapy is the only way to avoid nitrate tolerance.

- (2) **Rebound.** Intermittent use of nitrates is not associated with serious rebound of angina among patients taking maintenance therapy with β -blockers. Dosing to allow for a longer nitrate-free interval is also not associated with rebound.

4. **β -Blockers** (Table 6.4)

- a. **Mechanism of action.** Blocking the β_1 -adrenergic receptors in the heart decreases the rate–pressure product and oxygen demand. Decreased tension in the LV wall allows favorable redistribution of blood flow from the epicardium to the endocardium.
 - (1) Coronary vasospasm is rare from the β_2 -receptor blocking effect, but use of β -blockers should be avoided among patients with known, active vasospasm.
 - (2) β -Blockers have a variable degree of membrane-stabilizing effect.
- b. **Evidence for effectiveness.** β -Blockers decrease mortality after MI. The mortality benefit is not proven among patients with stable angina without prior MI, although symptomatic improvement is well documented.
- c. **Side effects.** The most important side effects are related to blockade of β_2 -receptors. However, data show that some of the side effects may occur less frequently than previously believed, and potentially lifesaving therapy should be offered to those at greatest risk for adverse events.
 - (1) Bronchoconstriction, masking of symptoms caused by hypoglycemic reaction among patients with diabetes, exacerbation of symptoms of peripheral vascular disease, and central nervous system (CNS) side effects such as somnolence, lethargy, depression, and vivid dreaming are well documented. The CNS side effects are thought to be related to the lipid solubility of these compounds.
 - (2) Symptomatic bradycardia and precipitation of heart failure are concerns for patients with a diseased conduction system and preexisting heart failure, respectively.
 - (3) Decreased libido, impotence, and reversible alopecia can be a problem for some patients.
 - (4) β -Blockers adversely alter lipid profile by increasing LDL cholesterol and decreasing HDL cholesterol.
- d. **Drug interactions.** Severe bradycardia and hypotension can occur with concomitant use of some calcium channel blockers.
- e. **Selection of preparations.** Cardiospecificity, lipid solubility, mode of excretion, and frequency of dosing are the main considerations when selecting a particular agent. The major cardiospecific agents (i.e., β_1 blockade) include metoprolol, atenolol, bisoprolol, and nebivolol. Of note, nebivolol also induces the endothelial NO pathway and contributes to vasodilation. Intrinsic sympathomimetic activity is not a clinically important factor in the choice of a medication, although benefits in patients with CAD have been decreased with agents having intrinsic sympathomimetic activity.
- f. **Effect on lipids.** The clinical significance of lipid abnormalities associated with β -blockers is unclear. β -Blockers have been associated with a decline in HDL level and a rise in triglycerides level. β -Blockers can improve survival among patients in New York Heart Association (NYHA) class I or II heart failure and angina. The condition of a patient with NYHA class III or IV disease should be stabilized before β -blocker therapy is instituted.

5. **Calcium channel blockers** (Table 6.5)

TABLE 6.4
 β -Blockers

Compound	Daily dose (mg)	Frequency	Excretion	Lipid solubility	Intrinsic sympathomimetic activity	Membrane stabilization
Selective β -blockers						
Metoprolol						
Short-acting	50–400	Every 12 h	Liver	Moderate		
Long-acting		Every 24 h			None	Possible
Atenolol	25–200	Every 24 h	Kidney	None	None	None
Acebutolol	200–600	Every 12 h	Kidney	Moderate	Low	Low
Nebivolol	5–40	Every 24 h	Kidney	High	None	
Betaxolol	20–40	Every 24 h	Kidney		Low	
Nonselective β (β_1 + β_2)-blockers						
Propranolol	80–320	Every 4–6 h	Liver			
Long-acting		Every 12 h		High	None	Moderate
Nadolol	80–240	Every 24 h	Kidney	Low	None	None
Timolol	15–45	Every 12 h	Liver	Moderate	None	None
Pindolol	15–45	Every 8–12 h	Kidney	Moderate	Moderate	Possible
Labetalol ^a	600–2,400	Every 6–8 h	Liver	None	None	Possible
Carvedilol ^a						
Short-acting	25–50	Every 12 h	Liver	Moderate	None	Possible
Long-acting	10–80	Every 24 h				

^aAlso a potent α_1 -antagonist.

TABLE 6.5 Calcium Channel Blockers						
Compound	Each dose (mg)	Frequency	Vasodilation	Sinoatrial node inhibition	Atrioventricular node inhibition	Negative inotrope
Nifedipine	30–120	Every 8 h	5	1	0	1
Nifedipine (Procardia XL)	30–180	Every 24 h				
Diltiazem	30–90	Every 6–8 h	3	5	4	2
Diltiazem (Cardizem CD)	120–300	Every 24 h				
Verapamil	40–120	Every 6–8 h	4	5	5	4
Verapamil (Calan SR and Isoptin SR)	120–240	Every 12 h				
Amlodipine (Norvasc)	2.5–10	Every 24 h	4	1	0	1
Felodipine (Plendil)	5–20	Every 24 h	5	1	0	0
Bepridil (Vascor)	200–400	Every 24 h	4	4	4	5
Isradipine (DynaCirc)	2.5–10	Every 24 h	4	4	0	0
Nicardipine (Cardene)	10–20	Every 8 h	5	1	0	0

0, no activity; 5, most potent effect. Intermediate numbers suggest intermediate potency of effects.

- a. **Mechanism of action.** These agents block calcium entry into vascular smooth muscle cells and cardiac cells by inhibiting calcium channels, but they do not affect the regulation of intracellular calcium release. The result is decreased contraction of muscle cells.
 - (1) The four types of calcium channels are L, T, N, and P.
 - (2) The T-type calcium channels are located in the atria and sinoatrial node and affect the phase I of depolarization.
 - (3) The L-type channels contribute to entrance of calcium into the cell during phase III of the action potential.
 - (4) The N and P types of channels are present mainly in the nervous system.
 - (5) The three main groups of calcium channel blockers are dihydropyridines (e.g., nifedipine), benzothiazepines (e.g., diltiazem), and phenylalkylamines (e.g., verapamil).
 - (6) The dihydropyridines bind to the extracellular portion of the L channels at a specific site. They do not bind to the T channels and do not have a negative chronotropic effect. Because of their extracellular site of action, dihydropyridines do not inhibit receptor-induced intracellular calcium release.
 - (7) Verapamil binds to the intracellular part of the L channel and inhibits the T channel. Intracellular calcium release is inhibited by verapamil because of its intracellular binding site and reflex sympathetic activation is less effective. Use dependence occurs with verapamil because open channels are needed for transport of the drug into the intracellular binding site. In stable angina, verapamil helps by improving rate–pressure product and by increasing oxygen delivery from coronary vasodilation.
- b. **Evidence of effectiveness.** Numerous placebo-controlled, double-blind trials have shown that calcium channel blockers decrease the number of anginal attacks and attenuate exercise-induced depression of ST segments.
 - (1) Studies comparing the efficacy of β -blockers and calcium channel blockers in the management of stable angina in which death, infarction, and unstable angina were used as end points showed calcium channel blockers to be as effective as β -blockers.
 - (2) Increased mortality caused by short-acting nifedipine among patients with CAD was demonstrated in a retrospective study and meta-analysis. If the use of nifedipine is contemplated, a long-acting preparation in conjunction with β -blocker therapy is the safer approach. The mechanism of increased mortality is unclear, but reflex tachycardia and coronary steal phenomenon are potential explanations.
- c. **Side effects.** The most common side effects are hypotension, flushing, dizziness, and headache. Because a negative inotropic effect can precipitate heart failure, the use of calcium channel blockers to treat patients with impaired LV function is relatively contraindicated. Conduction disturbances and symptomatic bradycardia occur with the use of compounds that have a marked inhibitory effect on the sinoatrial and atrioventricular nodes. Bepridil is known to prolong QTc, and QT monitoring is necessary when this medication is used. Lower extremity edema is often seen with the use of dihydropyridine calcium channel blockers and this may necessitate lowering the dose or discontinuation of the medication. The non-dihydropyridine calcium channel blockers are also known to cause constipation.
- d. **Drug interactions.** Digitalis levels are increased by the non-dihydropyridine calcium channel blockers verapamil and diltiazem. The use of these drugs is contraindicated in the presence of digitalis toxicity.
- e. **Selection of preparations.** Calcium channel blockers have a variable negative inotropic effect.

- (1) Amlodipine is most likely to be tolerated by patients with compensated heart failure. In decompensated heart failure, all calcium channel blockers should be avoided. Amlodipine is the only calcium channel blocker approved for angina by the US Food and Drug Administration (FDA).
 - (2) Patients with conduction disturbances should take agents with minimal effects on the conduction system. Longer acting preparations minimize the risk for precipitation of angina caused by reflex tachycardia.
- 6. ACE inhibitors.** The rationale for using ACE inhibitors to manage chronic stable angina comes from post-MI and heart failure trials that demonstrated a significant reduction in ischemic events with the use of ACE inhibitors.
- a. It is possible that ACE inhibitors, by decreasing mainly the preload and, to some extent, afterload, decrease myocardial oxygen demand and help in the management of chronic stable angina. The Heart Outcomes Prevention Evaluation (HOPE) trial in high-risk patients with CAD, stroke, diabetes, and peripheral vascular disease showed that ramipril was associated with a significant reduction in death, MI, and stroke in this population. A recent meta-analysis found that ACE inhibitors reduce the risk of these outcomes even in patients with atherosclerosis who do not have evidence of systolic dysfunction. It is notable that the randomized Prevention of Events with Angiotensin-Converting Enzyme Inhibition (PEACE) study evaluating the use oftrandolapril in patients with preserved LV function did not find a benefit with respect to death, MI, angina, revascularization, or stroke. Numerous hypotheses to explain these divergent results, including dose effects, difference in medication effects, and the risk level of enrolled patients, have been postulated. Nevertheless, the use of ACE inhibitors is recommended (class I) for patients with abnormal LV function and considered reasonable (class IIa) for patients with normal LV function.
 - b. The relative efficacy of different ACE inhibitors for relieving ischemia has not been well studied.
 - c. Serious side effects of ACE inhibitors include cough, hyperkalemia, and decreased glomerular filtration rate. They are contraindicated in the care of patients with hereditary angioedema or bilateral renal artery stenosis.
- 7. Hormone replacement therapy (HRT).** The lipid profiles of women change unfavorably after menopause. LDL, total cholesterol, and triglyceride levels increase and HDL level decreases. All these changes have an adverse effect on cardiovascular morbidity and mortality. Several large case-controlled and prospective cohort studies suggested that the postmenopausal use of estrogen alone or in combination with medroxyprogesterone acetate has a favorable effect on lipid profile and cardiovascular events. However, both the Women's Health Initiative (WHI) study on primary prevention and the Heart and Estrogen/progestin Replacement Study (HERS) on secondary prevention showed an increased risk of cardiovascular and cerebrovascular events in postmenopausal women receiving HRT. Another randomized trial quantifying coronary atherosclerosis angiographically showed negative results with respect to estrogen use. As a result, it has been postulated that the previously shown benefits might have been caused by the "healthy user" effect, and the use of HRT for primary prophylaxis against cardiovascular events is not recommended.
- a. **Benefits of use.** Although the use of estrogen has shown an increase in cardiovascular events, it is associated with some specific favorable findings. The positive effects of estrogen use include maintenance of normal endothelial function, reduction in levels of oxidized LDL, alteration in vascular tone, maintenance of normal hemostatic profile, a favorable effect on plasma glucose levels, reduction of osteoporotic fractures, and a reduction in menopausal symptoms.

- b. **Side effects** include bleeding, nausea, and water retention. Because doses of estrogen are small, these side effects are uncommon. For patients with an intact uterus, routine gynecologic examination is mandatory for cancer surveillance. The risk of breast cancer is also increased with the use of HRT, and routine screening is beneficial.
- 8. **Antioxidants.** The role of vitamins A, C, and E is unclear in patients with CAD.
 - a. The initial observational studies on the role of daily vitamin E supplementation in reducing the risk of cardiovascular events among patients with proven atherosclerotic heart disease appeared promising. However, when vitamin E was tested in a randomized fashion, no benefit in its use was proved. There are also data suggesting that vitamin E may attenuate the effect of statins. Vitamins A, C, and E are not recommended for the secondary prevention of cardiovascular events.
 - b. Data are lacking about vitamins A and C. Most of the available information suggests no benefit in taking supranormal doses of these vitamins. Vitamin A does not prevent LDL oxidation, even though it binds to LDL molecules. Because it is water soluble, vitamin C does not bind to the LDL molecule. These two vitamins are not recommended for the prevention of progression of atherosclerosis.
- 9. **Ranolazine**
 - a. Ranolazine has recently been shown to work by inhibiting the late sodium channel in myocytes, which can otherwise remain open in pathologic states such as ischemia and heart failure. By reducing the late sodium entry into myocytes, ranolazine causes reduced sodium-dependent calcium entry into the cytosol. This downstream reduction in intracellular calcium levels is thought to reduce diastolic stiffness, thereby improving diastolic blood flow and reducing ischemia and angina. Earlier studies had suggested that effects of ranolazine were primarily through its impact on fatty acid metabolism; however, the weight of evidence now suggests that late sodium channel inhibition is its primary mechanism.
 - b. Numerous randomized studies of ranolazine, with or without background antianginal therapy, have shown a benefit in patients with stable angina with respect to frequency of anginal attacks, exercise duration, time to ST-segment depression on treadmill testing, and use of sublingual nitroglycerin.
 - c. **Side effects.** Dizziness, headache, and GI intolerance are the most common side effects noted. Prolongation of the QT interval has been reported, especially in patients with hepatic or liver dysfunction due to decreased metabolism. **Prolonged QT interval** at baseline or during treatment follow-up **is a contraindication** to its use.
 - d. **Drug interactions.** Inhibitors of CYP3A4, such as azole antifungals, non-dihydropyridine calcium channel blockers, macrolide antibiotics, protease inhibitors, and grapefruit juice, should not be used concomitantly due to inhibition of ranolazine metabolism.
- 10. **Newer pharmacologic approaches**
 - a. Therapy with direct infusion of vascular endothelial growth factor (VEGF) and basic fibroblast growth factor proteins has been shown to increase collateral blood flow in animal models. Studies are underway to investigate the role of these agents in improving collateral blood flow to the ischemic myocardium of patients with angina. Although early results are encouraging, long-term risks and benefits of such therapy remain largely unknown.
 - b. Approaches involving the use of gene therapy to cause overexpression of these endogenous growth factors to control the development of collateral blood vessels have been proposed. These approaches are under investigation.

11. **Enhanced external counterpulsation (EECP)** has become a treatment option for patients with stable angina.
 - a. EECP involves the intermittent compression of the lower extremities in an effort to increase diastolic pressure and augment coronary blood flow. Three sets of balloons are wrapped around the lower legs, lower thighs, and upper thighs, with precise cuff inflation and deflation gated with the ECG. The lower cuffs are inflated at the start of diastole, as represented by the beginning of the T wave, and simultaneous deflation of all three chambers is triggered just before systole at the onset of the P wave.
 - b. In patients with refractory angina, clinical trials have demonstrated improvements in exercise tolerance, reduction in anginal symptoms, decreased use of nitroglycerin, and improvements in objective measures of ischemia as measured by thallium scintigraphy. These benefits are maintained at 2 years of follow-up.
- C. **Percutaneous coronary intervention.** The effectiveness of PCI to control symptoms in chronic stable angina and to prevent death or MI has been compared with medical management and CABG.
 1. **Compared with medical treatment**
 - a. The Angioplasty Compared with Medicine (ACME) trial compared PCI with medical therapy in approximately 200 patients with single-vessel and multivessel CADs. Patients with single-vessel CAD showed better symptomatic relief at 6 months with PCI but no difference in mortality or MI. Patients with two-vessel CAD had no significant differences in symptoms, mortality, or MI.
 - b. The Medicine, Angioplasty, or Surgery Study (MASS) randomized approximately 200 patients with proximal left anterior descending (LAD) artery disease to medical therapy, PCI, or CABG. This study demonstrated no difference in the primary end point (i.e., death, MI, or refractory angina necessitating revascularization). Patients randomized to CABG had a lower incidence of events compared with the other two groups, driven by a decrease in repeat revascularization procedures.
 - c. The Randomized Intervention Treatment of Angina-2 (RITA-2) trial randomized more than 1,000 patients with stable angina to medical therapy or PCI. After 2.7 years of follow-up, the primary end point (i.e., death or MI) was lower in the medically treated group. There was an improvement in angina, exercise capacity, and perceived quality of life in patients who underwent PCI. There was also a higher incidence of revascularization in the medically treated group.
 - d. The study on Optimal Medical Therapy (OMT) with or without PCI for Stable Coronary Disease (by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation [COURAGE] Trial Research group) evaluated patients with severe angiographic disease of one or more vessels, and either classic symptoms or documented ischemia on provocative testing. Compared with aggressive medical therapy, an initial strategy of PCI with BMS did not reduce the primary endpoint of death or major adverse cardiovascular events including symptom relief. Notable limitations to the interpretation of this study include the fact that the OMT group had stringent follow-up to achieve the high rates of medical adherence, one-thirds of patients in the medical therapy group crossed over to PCI (but were included in the OMT group as intention-to-treat analysis), and almost 80% of patients had no or minimal angina. Furthermore, it should be stressed that all patients were enrolled after angiography had been performed.
 - e. In a substudy of patients enrolled in COURAGE on the basis of positive stress imaging, investigators found that PCI in addition to OMT was

superior in reducing ischemia than OMT alone. Furthermore, the degree of residual ischemia was related to future risk of death or MI. The adequately powered ISCHEMIA trial has been funded by the National Heart, Lung, and Blood Institute to address this issue.

- f. The Occluded Artery Trial (OAT) tested the hypothesis that routine PCI of totally occluded arteries 3 to 28 days after MI in high-risk but asymptomatic patients would improve outcomes. In the 2,166 patients studied, there was no statistically significant difference in long-term cardiac events between the PCI and the medical therapy groups, although the PCI group had more rapid relief of angina.
 - g. The use of DES in comparison to BMS has significantly decreased the risk of in-stent restenosis and the need for target vessel revascularization, thereby improving quality of life, providing freedom from angina, and reducing the risk of repeat procedures. Acknowledging the slightly greater risk of ST with DES compared with BMS, the absolute risk of ST even with DES is quite low. Therefore, their use in appropriate situations is still highly considered in patients without bleeding issues, upcoming surgery, or financial constraints to long-term antiplatelet therapy.
- 2. Compared with CABG**
- a. The Emory Angioplasty versus Surgery Trial (EAST) randomized approximately 400 patients with multivessel disease to PCI or CABG. After 8 years of follow-up, there was no difference in the combined end point of mortality, Q-wave MI, and large thallium perfusion defect. In patients with proximal LAD artery disease or diabetes, there was a nonsignificant trend toward improved survival with CABG.
 - b. The Bypass Angioplasty Revascularization Investigators (BARI) conducted the largest trial comparing PCI with CABG in the management of multivessel disease. In this trial, there was no difference in survival between patients randomized to PCI or CABG at 7 years of follow-up, although the subgroup of patients with diabetes had a better survival rate with CABG than with PCI (76.4% vs. 55.7%).
 - c. The Arterial Revascularization Therapies Study (ARTS) randomized 1,200 patients with multivessel disease to CABG or BMS placement. After 1 and 5 years of follow-up, there was no difference in mortality, MI, or stroke. Outcomes were similar for patients with stable and unstable angina. Among diabetic patients, however, mortality was greater for those who received PCI. There was a greater incidence of repeat revascularization in the PCI group, although the use of DES in ARTS 2 (compared with the historic CABG group from ARTS 1) shows a similar 1-year rate of revascularization between PCI and CABG groups.
 - d. The surgery or stenting (SoS) study compared almost 1,000 patients with multivessel disease in the setting of ACS or non-ACS presentation. There was an increased mortality and need for repeat revascularization in the PCI group, which could not be attributed to a diabetic population.
 - e. In the BARI 2 Diabetes (BARI 2D) trial published more recently, investigators compared prompt revascularization (PCI or CABG as deemed appropriate) and OMT in a group of patients with type 2 diabetes mellitus and CAD. The primary outcome of death was not significantly different in the two groups, nor was the rate of major cardiovascular events (the major secondary end point including death, MI, and stroke). When stratified by revascularization strategy, patients in the CABG group had greater freedom from major cardiovascular events (77.6% vs. 69.5%, $p = 0.01$); this finding was not significant in patients undergoing PCI. Notably, however, this trial was not designed to compare CABG and PCI as revascularization strategies.

- f. The recently reported SYNERgy between PCI with TAXus and cardiac surgery (SYNTAX) was a pivotal trial randomizing patients with three-vessel disease or left main trunk (LMT) stenosis to multivessel PCI versus CABG. The primary end point of death, stroke, MI, and repeat revascularization favored CABG (12.3% vs. 17.6%, $p = 0.002$). The secondary end point which included death, stroke, and MI was not different between the two groups (7.7% vs. 7.6%, $p = 0.98$). The primary end point favoring CABG was therefore driven primarily by increased rates of repeat revascularization in the PCI group (13.5% vs. 5.9%, $p < 0.001$), though notably the rate of stroke was also significantly lower in the PCI group (2.2% vs. 0.6%, $p = 0.003$).
 - g. The other major take-home point of the SYNTAX trial was the formulation of the SYNTAX score, which received a class I indication for evaluation of LMT or multivessel disease in the most recent ACC/AHA PCI guidelines. The SYNTAX score grades coronary anatomy on the basis of lesion location, complexity, and functional impact and is a helpful tool for assessing patients at the individual level when discussing options of CABG versus PCI. In the trial, outcomes were assessed by SYNTAX score tertile: patients with a low (0 to 22) or intermediate (23 to 32) score had no difference between the two modes of revascularization for the primary outcome. In patients with a score > 32 , however, CABG was favored for the primary outcome (10.9% vs. 23.4%, $p < 0.001$).
 - h. In patients with LMT stenosis, guidelines had long recommended CABG as the treatment of choice. However, in the modern era of stent placement, PCI of “unprotected” LMT stenosis has gained favor. The 2011 ACC/AHA PCI Guidelines revised the previous class III recommendation for unprotected LMT PCI to class IIa.
 Small studies have shown that the mortality difference between PCI and CABG in similarly matched groups of patients is negligible. Furthermore, recent studies comparing the experience of DES implantation in LMT with BMS placement have shown a marked decrease in the need for repeat revascularization.
 - i. In the prespecified subgroup of patients undergoing unprotected LMT PCI versus CABG in the SYNTAX trial, the primary outcome was similar between the two groups. As in the main study population, stroke was higher in the CABG group (2.7 vs. 0.3%, $p = 0.009$) and repeat revascularization was higher in the PCI group (11.8 vs. 6.5%, $p = 0.02$). Given the clinical equipoise that surrounds unprotected LMT revascularization, the EXCEL (Evaluation of Xience Prime versus Coronary Artery Bypass Surgery for Effectiveness of Left Main Revascularization) trial is currently underway. The investigators plan to randomize 2,500 patients with LMT stenosis and a SYNTAX score < 32 to PCI versus CABG.
 - j. At present, strong consideration is given to CABG in the group of patients with multivessel disease and diabetes, LV dysfunction, or LMT disease who are able to undergo open heart surgery. In the general population with multivessel or LMT disease, however, there is a paucity of evidence showing a survival advantage to CABG over PCI, and recent trials with modern treatment practices (including DES implantation, aggressive antiplatelet therapy, off-pump coronary artery bypass procedures, and use of arterial grafts) have shown favorable comparisons between the two treatment strategies. For patients who are able to undergo either of the treatments, an educated decision should be made by the patient, the cardiologist, and a cardiac surgeon.
3. **Revascularization methods.** For details of PCI strategy and equipment, please refer **Chapter 65**.

D. Coronary artery bypass grafting

1. **Compared with medical treatment.** Compared with medical treatment, CABG improves the survival rate among patients with high-risk stable angina. The benefit is most profound in patients with three-vessel CAD, impaired LV function, or substantial LMCA stenosis.
 - a. This information is derived from the Coronary Artery Surgery Study (CASS), European Coronary Surgery Study (ECSS), and Veterans Administration Cooperative Study (VACS). These trials were completed before generalized awareness grew regarding the benefits of medical management with β -blockers, ACE inhibitors, antiplatelet agents, or lipid-lowering medications.
 - b. Surgical techniques have also changed significantly, with greater use of arterial conduits including internal mammary artery (IMA) grafts, minimally invasive surgery, and improved techniques of cardiac tissue preservation and anesthesia.
2. **Venous or arterial grafts.** There are different techniques of CABG. The use of minimally invasive bypass surgery involving the left internal mammary artery (LIMA) in patients with isolated LAD artery stenosis has not shown any difference in the rate of mortality, MI, or stroke in comparison to PCI but has shown a decrease in the need for repeat revascularization. With open sternotomy, in which the use of LIMA is well studied, mammary arterial grafting has better long-term outcome compared with vein graft conduits. Given the success of the (LIMA) graft, other arterial conduits have been used, such as the right internal mammary artery (RIMA), the radial artery, and the right gastroepiploic artery.
 - a. Twenty percent of venous grafts are nonfunctional at 5 years and only 60% to 70% are functional after 10 years. In contrast, > 90% of LIMA to LAD artery grafts are patent 20 years after the operation.
 - b. **Internal mammary artery** grafts have a better patency rate at 10 years when used for LAD lesions (95%) than for circumflex (88%) or right coronary artery (76%) lesions. The patency rates are higher for LIMA compared with RIMA and for in situ grafts compared with free grafts.
 - c. Patient survival is better with an IMA graft than when only saphenous venous grafts are used. This survival benefit persists for up to 20 years.
 - d. The use of bilateral IMA grafts appears promising, with evidence that the use of RIMA in addition to LIMA improves survival in comparison to LIMA plus saphenous vein grafting. The use of RIMA is technically difficult, however, and has, therefore, not been widespread.
 - e. The radial artery graft was introduced into clinical practice around the year 1970 and initially had mixed results. However, at approximately 1 year, 92% of the grafts are patent and at 5 years 80% to 85% of grafts are open. The right gastroepiploic arterial graft has been in use for approximately 15 years, and a 5-year angiographic patency rates of 92% has been reported.
3. **Previous CABG.** Little information is available on the treatment of patients who have already undergone bypass surgery and have stable angina. Although another bypass operation may be offered to these patients, direct comparison with medical treatment in this patient population has not been made. The use of multiple arterial grafts at the time of first CABG reduces the need for reoperation.
4. **Compared with PCI.** This is discussed in Section IV.C.

E. Other forms of revascularization

Percutaneous and intraoperative transmyocardial revascularization are potential treatments for patients with coronary disease not amenable to PCI or CABG. Some reports suggest improvement in symptoms, a decrease in perfusion defects, and improvement in contractile function after these procedures but no survival benefit

has been reported. This procedure should be reserved as palliation for patients with medically refractory angina and no other revascularization option, but it has generally fallen out of favor in recent years.

Promotion of ancillary blood vessels by means of injection of blood vessel–promoting agents such as VEGF at the time of surgical or percutaneous coronary revascularization is currently under investigation. So far, the results of this form of intervention have been mixed. Smaller studies targeting improvement in perfusion and exercise tolerance suggest some benefit in the active treatment group. However, two, somewhat larger, studies have recently been terminated early due to lack of benefit at interim analysis.

F. Lifestyle modification

1. Exercise

- a. **Rationale.** Exercise conditions the skeletal muscles, which decreases total body oxygen consumption for the same amount of workload. Exercise training also lowers heart rate for any level of exertion, which decreases the oxygen demand on the myocardium for any workload. Some evidence shows that higher physical activity and exercise can decrease cardiovascular morbidity and mortality.
 - b. **Recommendation.** For secondary prevention, aerobic and isotonic exercises with a goal of achieving a sustained heart rate of approximately 70% to 85% of the maximum predicted heart rate at least 3 or 4 times per week has been shown to improve survival. For beginners, a supervised exercise or rehabilitative program, in which 50% to 70% of maximal predicted heart rate is achieved, is also helpful. Isometric exercises are not recommended because they increase myocardial oxygen demand substantially.
2. **Diet.** A low-fat diet that includes cereals and grains, skimmed dairy products, fruits and vegetables, fish, and lean meats should be recommended and this is effective in providing cardiovascular risk reduction in patients with CAD. These are also integral components of the “Mediterranean Diet,” which has been shown to reduce cardiovascular risk. A multidisciplinary approach to the care of patients with CAD that includes a nutritionist/dietician can be quite helpful in personalizing patients’ eating habits.
 3. **Smoking cessation.** Cigarette smoking is associated with progression of atherosclerosis, increased myocardial demand due to an α -adrenergic increase in coronary tone, and adverse effects on hemostatic values, all of which can lead to worsening of stable angina. Smoking cessation decreases cardiovascular risk among patients with established CAD, including patients who have undergone CABG. Physician counseling is the best approach to achieve this goal and adjunctive therapies include nicotine replacement patches, gum, or sprays, or medications such as bupropion and varenicline.
 4. **Psychological factors.** Anger, hostility, depression, and stress are shown to adversely affect CAD. Results of small, nonrandomized trials show that biofeedback and various relaxation techniques can help modify these factors.

V. RECOMMENDED APPROACH TO STABLE ANGINA

- A. The following approach is suggested for the treatment of patients with stable angina.
 1. It is reasonable to risk stratify patients with stable angina using stress testing with imaging, such as nuclear isotope imaging or echocardiography.
 - a. LV systolic function should be assessed with echocardiography to guide therapy and to identify patients with moderate LV systolic dysfunction.
 - b. Patients with small perfusion defects or small wall-motion abnormalities, high threshold for ischemia, normal LV systolic function, and clear symptoms should be treated with medication.

2. If symptoms continue after medical therapy is maximized, angiography should be planned. Coronary angiography should also be performed for patients with evidence of impaired perfusion involving multiple territories, a low threshold for ischemia, and moderate LV systolic dysfunction.
3. **Single-vessel disease.** If a patient has single-vessel CAD that does not involve the LMT or supply a large myocardial territory, medical management with risk factor modification is the appropriate first step.
 - a. If patients cannot tolerate medical treatment or have symptoms despite maximum medical therapy, revascularization therapy should be offered.
4. Among patients with **multivessel CAD**, medical treatment remains an alternative for patients who have normal LV systolic function, mild symptoms, and relatively smaller areas of myocardium at risk.
 - a. The decision for multivessel PCI versus CABG in this group of patients should be made on an individual basis, taking into consideration the angiographic anatomy, LV function, patient comorbidities, surgical risk, and patient preference.
 - b. Any doubt regarding viability of the myocardium at risk should be addressed with appropriate diagnostic studies before revascularization.
5. In patients with “unprotected” LMT stenosis, the previous recommendations of CABG in all patients who are able to undergo surgery have recently been revised. PCI for severe LMT disease may be appropriate in select patients.
6. Regardless of treatment strategy, aggressive risk factor modification, including use of lipid-lowering agents, lifestyle modification, and aspirin therapy, is an essential component of management.

ACKNOWLEDGMENT: *The authors thank Dr. Keith Ellis for his contributions to earlier editions of this chapter.*

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Other Ischemic Syndromes: Silent Ischemia and Syndrome X

SILENT ISCHEMIA

- I. **INTRODUCTION.** Silent ischemia represents an underappreciated manifestation of coronary artery disease (CAD), occurring in up to 20% to 40% of patients with stable and unstable coronary syndromes. It is estimated that 195,000 silent first myocardial infarctions (MIs) occur each year, which assumes that 21% of MIs are silent. By definition, patients are asymptomatic, lacking typical or atypical anginal symptoms. Silent ischemia may be documented by a variety of diagnostic modalities, including resting electrocardiogram (ECG), ambulatory ECG (AECG), nuclear scintigraphy, and echocardiography.
- II. **CLINICAL PRESENTATION.** Patients may be loosely categorized into three groups, collectively representing a continuum of silent ischemia.
 - A. **Type I** have **asymptomatic** ischemia with no known CAD history with **asymptomatic** MI patterns. Clinicians may discover evidence of subclinical MI from a resting ECG or a preoperative stress test. In the Framingham study, 12.5% of patients with MI had an unrecognized “silent” infarction. Patients may also present with arrhythmias or sudden death from subsequent scar. These patients are considered to have an ineffective “anginal warning system.”

In addition, a subset of this group includes patients with **asymptomatic** ischemia without a history of infarction. Silent ischemia is often discovered by stress tests after referral for aggressive primary screening. This type of screening may occur in patients with diabetes, strong family histories, or a high-risk electron beam computed tomography (EBCT) result. Given the increasingly technological nature of medical culture, the prevalence of these patients is likely to rise. AECG is rarely used as a primary screening modality. The American College of Cardiology and American Heart Association (ACC/AHA) guidelines consider the use of AECG for ischemia monitoring in asymptomatic individuals as a class III recommendation.
 - B. **Type II** have **symptomatic** MIs but subsequent **asymptomatic** ischemic syndromes. Ischemia is often missed because of a lack of symptoms. Patients in this category are most often encountered after a positive stress test or the rarely ordered AECG. Type II patients may have an abnormal **pain threshold**.
 - C. **Type III** encompass the largest patient population with silent ischemia. These patients with known CAD have both **symptomatic** and **asymptomatic** ischemia. Between 20% and 40% of patients with chronic anginal symptoms have silent ischemia. About 75% of ischemic episodes are silent and only 25% are symptomatic.
- III. **DIAGNOSTIC TESTING.** Most patients with silent ischemia are either never identified or identified retrospectively. In the Asymptomatic Cardiac Ischemic Pilot (ACIP) study, patients with frequent silent ischemic events were found to be at increased risk for advanced

coronary disease, including high-risk coronary anatomy such as three-vessel disease. Currently, testing to detect ischemia in asymptomatic patients is controversial. The ACC/AHA guidelines consider the use of exercise ECG testing (without imaging) in asymptomatic patients with possible myocardial ischemia on AECG or severe coronary calcification on EBCT as a *class IIb recommendation*. The use of exercise plus imaging stress testing (echo and nuclear) in asymptomatic patients with a low-risk Duke treadmill score on exercise ECG testing is a *class III recommendation*. In patients with an intermediate- or high-risk Duke treadmill score, it is a *class IIb recommendation*. In asymptomatic patients with prior revascularization with high-risk features, periodic stress testing is a *class IIb recommendation*.

IV. MECHANISMS

- A. **The exact explanation** for a lack of symptoms in the face of unequivocal ischemia remains **unknown**. It likely represents abnormal modulation of cardiac **pain perception at different levels in the afferent pathway of the heart**.
- B. **The association between diabetes and silent ischemia and painless infarction** has been attributed to **autonomic neuropathy**. A higher threshold for pain has been related to increased baseline plasma β -endorphin levels and increased age. A potential connection exists between baroreceptor function and pain perception. This may explain the relationships among increased systolic blood pressure, reduced sensitivity to ischemic pain, and the demonstration of anginal relief with carotid sinus stimulation. Results of one study suggested that the gating of afferent signals at the thalamic level is a potential mechanism for silent ischemia. Patients with symptoms had activation of basal frontal, anterior, and ventral cingulate cortices and the left temporal pole. **Cortical activation was limited to the right frontal region in patients with silent ischemia**. It also has been proposed that, among type III patients, asymptomatic ischemia may represent shorter and less severe episodes compared with symptomatic episodes.

V. MANAGEMENT

- A. **Medications** effective in preventing symptomatic ischemia (i.e., nitrates, calcium antagonists, and β -blockers) and in decreasing myocardial O_2 demand are also effective in reducing or eliminating episodes of silent ischemia. In one randomized study, metoprolol was found to be better than diltiazem in reducing the mean number and duration of ischemic episodes. However, the combination of calcium antagonists and β -blockers was more effective than either agent alone. Lipid-lowering therapy has also shown a reduction of ischemia on AECG. The ACC/AHA guidelines currently regard the use of ASA (aspirin), β -blockers, angiotensin-converting enzyme inhibitors, and statins as class I recommendations in asymptomatic patients with evidence of previous MI and class IIa recommendations in patients without history of previous MI. It has also been postulated that ranolazine may also reduce ischemia before symptoms become present.
- B. **The goal of therapy remains controversial**. It is not clear whether therapy should be guided by ischemia or angina. The ACIP study revealed no difference in benefit from either of these approaches. However, 2-year follow-up data from this study demonstrated improved prognosis with initial revascularization compared with angina- or ischemia-guided medical therapy. The Swiss Interventional Study on Silent Ischemia type I (SWISSI I) randomized 54 type I subset patients to treatment with antianginal medications and aspirin versus risk factor modification only. Their findings showed that treatment with the combination of antianginal drug therapy and aspirin appeared to significantly reduce cardiac events, including cardiac death, nonfatal MI, or acute coronary syndrome. In addition, these patients had consistently lower rates of exercise-induced ischemia during follow-up. The SWISSI II study randomized 201 patients with type II silent ischemia to percutaneous coronary intervention (PCI) versus ongoing anti-ischemic medical therapy. The results showed a significant decrease in rates of cardiac death, nonfatal MI, and subsequent

need for revascularization in patients in the PCI group over a 10-year follow-up period. Similarly, in patients with type I silent ischemia, with an ineffective “anginal warning system,” it has been suggested that it may be reasonable to treat silent ischemia in a manner equivalent to that for symptomatic ischemia in the general population in terms of revascularization and medical therapy.

VI. PROGNOSIS. Myocardial ischemia, whether symptomatic or asymptomatic, is associated with poorer outcomes among patients with CAD. Patients with frequent and accelerating episodes of ST-segment depression on AECG monitoring are at higher risk for subsequent cardiac events than patients with few or no such episodes. The Copenhagen Holter study examined the significance of ischemic changes on AECG in asymptomatic, healthy individuals between the ages of 55 and 75 years (type I subset). They found that patients with silent ischemia had a threefold higher risk of subsequent cardiac events over a 5-year follow-up period. Circadian effects of asymptomatic ST depression on AECG have been noted with changes being more common in the morning hours; however, nocturnal ST-segment changes have been associated with multivessel CAD or left main narrowing. It has not been proven conclusively, however, that detection of silent ischemia is an independent risk factor for future cardiac events.

VII. CONTROVERSIES

- A. Patients with silent ischemia on AECG monitoring represent heterogeneous populations. This may be a marker of unstable, complex coronary plaque or microvascular dysfunction. Results of the angiographic substudy of the ACIP study suggested that most patients with silent ischemia have proximal coronary lesions or complex coronary plaques. This hypothesis has not been tested in a larger population and continues to be investigated.
- B. The potential role of **AECG monitoring** for ischemia still needs to be determined to assess its utility compared with more commonly used tests, such as exercise testing with thallium imaging. Different populations should be carefully examined at specific times after their events to answer these questions. Currently, the exercise ECG test remains the most useful and validated screening test for significant CAD.
- C. **Medical therapy** should be used to decrease or eliminate ischemia; however, the relative role of medical therapy compared with revascularization in asymptomatic patients with demonstrable ischemia remains unclear.
- D. **Coronary artery calcium** scanning to screen asymptomatic patients for CAD is now a *class IIa indication* in those patients with an intermediate (10% to 20%) 10-year risk of cardiac events based on the Framingham risk score or other global risk algorithm and for asymptomatic patients aged 40 years and older with diabetes mellitus.

SYNDROME X

- I. **INTRODUCTION.** Syndrome X is defined as the constellation of effort-induced **anginalike discomfort** in the setting of **angiographically normal coronary arteries** (without inducible spasm on ergonovine provocation testing). This chest pain is usually indistinguishable from traditional ischemic angina caused by obstructive coronary disease and is, therefore, considered a diagnosis of exclusion.
- II. **PRESENTATION.** In the clinical setting, syndrome X is a diagnosis given to patients with persistent **anginal symptoms**, often with abnormal stress testing despite a **normal angiogram** and **negative workup** for noncardiac chest pain. Up to 25% of all coronary angiograms performed in the United States for symptoms of chest pain are normal; yet, most cardiologists do not routinely use ergonovine provocation or intravascular ultrasound to evaluate for variant angina or angiographically silent coronary atherosclerosis in this subset of patients. When intravascular ultrasonography studies have been performed

in these patients, a spectrum of findings ranging from normal vessels to intimal thickening to nonobstructive atheromatous plaque has been reported. Syndrome X has an increased occurrence in women (3:1 preponderance), both premenopausal and postmenopausal. Of note, abnormal cardiac physical examination findings and left ventricular (LV) dysfunction on stress testing are both uncommon in syndrome X.

III. ETIOLOGY AND PATHOPHYSIOLOGY. Syndrome X represents a heterogeneous population and may represent multiple processes with varying causes. **Endothelial dysfunction, microvascular ischemia, and abnormal pain perception have all been implicated in the genesis of this disorder.** Endothelial dysfunction as demonstrated by abnormal coronary flow reserve (CFR), single positron emission computed tomography stress, and positron emission tomography stress testing is common in these patients. In addition, behavioral and psychiatric conditions often coexist. Specific treatment aimed at managing behavioral issues may lead to symptomatic improvement in chest pain in some patients.

IV. DIAGNOSTIC TESTING. Because syndrome X is a **diagnosis of exclusion**, both traditional obstructive coronary atherosclerosis and causes of noncardiac chest pain must be ruled out before a final diagnosis can be made. Multislice computed tomography angiography may play an increasingly important role in avoiding invasive angiography in some of these patients. Laboratory testing for endothelial dysfunction is not widely utilized in the clinical setting. Abnormal CFR in the catheterization laboratory can help confirm abnormalities in microcirculatory control, often accompanied by endothelial dysfunction in patients with syndrome X. C-reactive protein (high-sensitivity CRP) has been shown to correlate with the severity of symptoms and ECG changes in this population.

V. THERAPY. The **primary goal** of the therapy should be **aggressive cardiac risk factor modification**, including lifestyle changes and lipid treatment, although the **ideal treatment regimen is unknown**. β -Blockers have been shown to be very effective in controlling anginal symptoms in this population and are considered superior to calcium channel blockers and nitrates. Other treatments that have provided benefit include tricyclic antidepressants (imipramine), oral aminophylline, and estrogen in postmenopausal women. Given the recent data on estrogens, caution should be exercised when considering estrogen therapy in patients with suspected syndrome X.

VI. PROGNOSIS. The prognosis for patients with angina and normal coronary arteriograms is generally favorable with good long-term outcomes shown in multiple studies. However, subsets of these patients such as patients with persistent anginal symptoms and/or evidence of significant myocardial ischemia on stress testing seem to be at higher risk and have significantly higher event rates, including premature death, MI, and stroke, than the baseline population. These subsets of patients should be treated aggressively with risk factor modification and counseled regarding lifestyle modification.

VII. OTHER. Although not clearly related to syndrome X, **Takotsubo syndrome** (aka LV apical ballooning syndrome and stress-induced cardiomyopathy) is a condition that has been receiving increasing attention. Clinical features include sudden onset of chest pain, ECG changes (often ST elevation) mimicking an acute MI, usually in the setting of severe emotional distress and catecholamine surge. The angiogram shows normal coronary arteries, and diagnosis is made on the typical appearance seen on LV ventriculogram or echocardiogram with basal hyperkinesis and severe apical systolic wall motion abnormality. Most patients recover LV function and require only hemodynamic and pharmacologic support.

ACKNOWLEDGMENTS: *The author and editors would like to thank Apur R. Kamdar, Tim Williams, and Marc S. Penn for their contributions to the previous version of this chapter.*

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SECTION



Heart Failure and Transplant

EDITOR

W.H. Wilson Tang

Heart Failure with Systolic Dysfunction

I. INTRODUCTION

A. **Heart failure** is a complex clinical syndrome characterized by impaired myocardial performance and progressive maladaptive neurohormonal activation of the cardiovascular and renal systems leading to circulatory insufficiency and congestion. Currently, acute heart failure syndromes (AHFS) constitute the most common indication for hospitalization in adults over age 65. With the increasing age of the population, improved survival of patients with acute coronary syndromes, and reduced mortality from other diseases, the incidence and attendant cost of managing patients with heart failure will inevitably increase.

B. Terminology

1. Based on the hemodynamic model, **systolic heart failure** has been defined by the presence of impaired contractility of the left ventricle, most commonly conveyed in an ejection fraction (EF) of < 40% to 50%. This drop in contractility may be associated with chamber dilation and a decreased stroke volume (Fig. 8.1). There is a growing appreciation for the limitations of this classification. The threshold for systolic dysfunction is arbitrary and it is now clear that patients with heart failure with preserved EF suffer similar morbidity and mortality. There is substantial variability in EF determinations made by different imaging modalities. Most importantly, EF correlates poorly with symptoms, cardiac indices, and potential response to pharmacotherapy.
2. In practice, heart failure is a bedside diagnosis that is defined by clinical assessment. Patients may have cardiac dysfunction without symptoms, often referred to as **asymptomatic left ventricular (LV) dysfunction**. Others may have preserved LV systolic function with typical signs and symptoms of heart failure, best referred to as **heart failure with preserved EF** (see Chapter 9).
3. The major pathophysiologic process in the progression of heart failure is **cardiac remodeling**, in the form of progressive chamber enlargement with an obligatory reduction in EF. Histopathologically, this is associated with myocyte hypertrophy, apoptosis, and necrosis. Molecular alterations including reexpression of a fetal gene program and alterations in excitation–contraction coupling and regulatory proteins occur.
4. In some cases, **myocardial recovery** or **reverse remodeling** is possible with pharmacologic and device therapy.
5. The term **congestive heart failure** is overused and nonspecific, often being applied to states of hypervolemia unrelated to cardiac dysfunction. Conversely, not all patients with heart failure have signs and symptoms of congestion.
6. The term **right heart failure** is used to describe patients with predominantly peripheral signs and symptoms of heart failure with a relative paucity of pulmonary congestion.
7. **Acute decompensated heart failure** or **AHFS** refer to episodes of acute or subacute deterioration of heart failure due to a wide range of precipitants. The vast majority of these events are marked by systemic and pulmonary congestion.

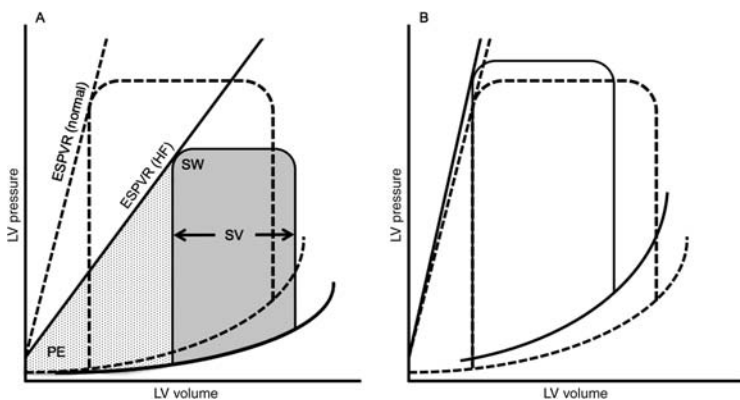


FIGURE 8.1 Pressure–volume loops in normal (dashed line) and heart failure (HF; solid line) patients. **A:** Pressure–volume loops in HF with impaired ejection fraction typically demonstrate a reduction in the end-systolic pressure–volume relationship (ESPVR; i.e., the end-systolic elastance), a representation of contractility. This is typically accompanied by an increase in end-diastolic volume and a reduction in stroke volume (SV) and stroke work (SW; shaded area). At a given ESPVR, a reduction in end-systolic pressure results in an increased SV and reduction in the left ventricular (LV) elastic potential energy (PE; speckled area). **B:** In contrast, patients with HF with preserved ejection fraction have a normal or elevated ESPVR with a left and upward shift in the end-diastolic pressure–volume relationship reflecting decreased myocardial compliance.

II. PATHOGENESIS

- A. Heart failure is a progressive disorder initiated by some form of myocardial injury.** This injury may range from acute disruptions in myocardial function (myocardial infarction or myocarditis) to one of a number of chronic derangements including familial and metabolic cardiomyopathies or chronic volume or pressure loading related to valvulopathies, intracardiac shunts, or systemic hypertension. Regardless of the initial insult, the compensatory mechanisms that may be beneficial acutely ultimately become maladaptive in the chronic phase.
- B. Neurohormonal activation**
 - 1. Activation of the sympathetic nervous system.** Chronic activation of the sympathetic nervous system ultimately results in decreased β -adrenergic receptor responsiveness and decreased norepinephrine stores and sympathetic innervation of the myocardium. Chronically, these changes contribute to myocyte hypertrophy, fibrosis, and necrosis. Extracardiac effects include increased tubular reabsorption of sodium, activation of the renin–angiotensin system (RAS), neurogenic vasoconstriction, and vascular hypertrophy.
 - 2. Activation of the RAS.** As heart failure progresses, renal hypoperfusion and sympathetic stimulation of the kidneys result in increased production of renin by the juxtaglomerular apparatus. Renin cleaves circulating angiotensinogen into the biologically inactive angiotensin I, which is subsequently cleaved by angiotensin-converting enzyme (ACE) to the biologically active angiotensin II. Importantly, angiotensin II can be generated in renin and ACE-independent pathways as well. In addition to direct cardiovascular effects, angiotensin II stimulates aldosterone production by the zona glomerulosa of the adrenal cortex, which in turn promotes reabsorption of sodium in exchange for

potassium in the distal nephron. Chronically, aldosterone results in the promotion of hypertrophy and fibrosis in the vasculature and myocardium, endothelial dysfunction, and inhibition of norepinephrine uptake.

3. **Other neurohormonal derangements.** Inappropriate production of arginine vasopressin has an antidiuretic effect contributing and worsens vasoconstriction. Endothelin, neuropeptide Y, and other peripheral vasoconstrictors further enhance vascular tone.

III. CLASSIFICATION

- A. The American College of Cardiology and the American Heart Association (ACC/AHA) guidelines currently classify heart failure on the basis of the evolution of the disease across a continuum:
 1. **Stage A:** patients at high risk for developing heart failure without structural heart disease or symptomatic heart failure.
 2. **Stage B:** patients with structural heart disease who have not yet developed symptoms of heart failure.
 3. **Stage C:** patients with structural heart disease with prior or current symptoms of heart failure.
 4. **Stage D:** patients with refractory end-stage heart failure who require specialized advanced treatment.
- B. The **New York Heart Association (NYHA) functional classification**, although subjective and vague, remains the most commonly used standard by which the severity of functional impairment is graded (Table 8.1).
- C. The **Killip classification** grades the severity of signs of decompensated heart failure in the post-acute coronary syndrome setting and is highly predictive of 30-day mortality.

- VI. **ETIOLOGY.** It is essential to make every effort to identify the specific etiology of heart failure as it may have implications for management and prognosis. While ischemic cardiomyopathy is by far the most common cause of systolic heart failure, a diverse array of disease states can culminate in this phenotype (Table 8.2).

TABLE 8.1

New York Heart Association Functional Classification

Class	Description
I	Patients have cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnea, or anginal pain.
II	Patients have cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitations, dyspnea, or anginal pain.
III	Patients have cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitations, dyspnea, or anginal pain.
IV	Patients have cardiac disease resulting in an inability to carry on any physical activity without discomfort. Symptoms of cardiac insufficiency or of the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

TABLE 8.2 Etiologies of Heart Failure

Dilated cardiomyopathy
Idiopathic
Familial
Hypertrophic cardiomyopathy
Restrictive cardiomyopathy
Unclassified cardiomyopathies
Fibroelastosis
Mitochondrial cardiomyopathy
Left ventricular noncompaction
Specific cardiomyopathies
Ischemic cardiomyopathy
Stress-induced cardiomyopathy
Valvular obstruction or insufficiency
Hypertensive
Inflammatory (lymphocytic, eosinophilic, giant cell myocarditis)
Infectious (Chagas disease, Lyme disease, HIV, enterovirus, adenovirus, CMV, bacterial or fungal infections)
Metabolic
Endocrine (thyroid diseases, adrenal insufficiency, pheochromocytoma, acromegaly, diabetes mellitus)
Familial storage disease (hemochromatosis, glycogen storage disease, Hurler's syndrome, Anderson-Fabry disease)
Electrolyte deficiency syndromes (hypokalemia, hypomagnesemia)
Nutritional deficiencies (kwashiorkor, anemia, beriberi, carnitine and selenium deficiency)
Amyloid
Familial Mediterranean fever
Systemic diseases
Connective tissue disorders (SLE, polyarteritis nodosa, rheumatoid arthritis, scleroderma, dermatomyositis, polymyositis, sarcoidosis)
Muscular dystrophies (Duchenne's, Becker's, myotonic, limb girdle)
Neuromuscular (Friedreich's ataxia, Noonan's disease)
Toxins (alcohol, catecholamines, cocaine, anthracyclines and other chemotherapeutics, radiation)

CMV, cytomegalovirus; HIV, human immunodeficiency virus; SLE, systemic lupus erythematosus.

Modified from WHO Classification.

- A. Ischemic cardiomyopathy** is the cause of 60% to 75% of cases of systolic heart failure in industrialized countries. It is defined as **cardiomyopathy in the presence of prior extensive myocardial infarction, hibernating myocardium, or severe coronary artery disease**. However, the mere *presence of obstructive coronary artery disease does not equal ischemic cardiomyopathy as it is possible to have coronary artery disease superimposed with a nonischemic etiology of heart failure*. A careful assessment of the coronary anatomy, the burden of ischemia, and the presence of infarcted and viable myocardium must be made and an assessment of the proportionality of these findings to the degree of myocardial dysfunction should be made. The risks and benefits of percutaneous or surgical revascularization should be assessed in all patients with ischemic cardiomyopathy. Extensive observational data have suggested a benefit for coronary artery bypass grafting (CABG) compared with medical therapy alone in moderate to severe LV systolic dysfunction. Registry data suggest that CABG is superior to percutaneous coronary intervention in patients with reduced EF. However, recently released 5-year data from the Surgical Treatment for Ischemic Heart Failure (STICH) trial demonstrated no difference in 5-year mortality for patients with left ventricular ejection fraction (LVEF) < 35% undergoing CABG in addition to optimal medical therapy versus optimal medical therapy alone. Furthermore, a substudy of STICH demonstrated that preoperative viability testing did not effectively predict whether patients derived benefit from CABG. Notably, patients with left main trunk disease and severe angina were excluded from the study and these patients should continue to be treated aggressively with revascularization.
- B. Dilated cardiomyopathy.** In 20% to 30% of cases of heart failure with systolic dysfunction, the precise etiology is not established and a diagnosis of nonischemic, dilated, or idiopathic cardiomyopathy is made. Patients with **dilated cardiomyopathy typically have a better prognosis than their ischemic counterparts**.
1. Dilated cardiomyopathy is frequently attributed to the residual effects of **subclinical viral myocarditis**. Reverse transcription polymerase chain reaction analysis of endomyocardial biopsies from patients with dilated cardiomyopathy demonstrates amplification of viral genomes in approximately two-thirds of cases. Any virus can cause myocarditis, but, owing to its ubiquity, coxsackie B virus is the most epidemiologically important.
 2. **Familial dilated cardiomyopathy.** It is now recognized that 25% to 50% of cases of dilated cardiomyopathy may have a genetic basis. Conditions are typically autosomal dominant and show variable penetrance. A detailed three-generation family history is essential at the time of initial evaluation. If the family history suggests a genetic predisposition, clinical screening of family members is appropriate and genetic testing can be performed following referral to a genetic counselor. Importantly, only 15% to 25% of presumed familial dilated cardiomyopathies have identifiable genetic alterations.
- C. Hypertensive and diabetic cardiomyopathy** are seldom considered as stand-alone diagnoses. Progression from LV hypertrophy to overt dysfunction in hypertensive patients (the so-called burnt-out hypertensive heart) most likely results from progressive microvascular ischemia. Hypertension and diabetes also contribute significantly to the development of coronary artery disease and ischemic cardiomyopathy.
- D. Cardiotoxic agents.** The list of toxins that can produce cardiomyopathy is extensive. Identification of the toxin and removal of the offending agent may halt the progression of or even reverse LV dysfunction.
1. **Chemotherapeutic agents.** **Anthracycline** toxicity can cause myocyte destruction and cardiomyopathy. Patients who receive a cumulative doxorubicin equivalent dose of < 400 mg/m² are at low risk for this syndrome, while those receiving a cumulative dose > 700 mg/m² have an approximately 20% lifetime risk of developing cardiomyopathy. Other cardiotoxic drugs that require careful cardiac monitoring include **cyclophosphamide** and **trastuzumab**. Trastuzumab

(Herceptin) is now frequently used in the treatment of human epidermal growth factor receptor 2 positive breast cancer and has been associated with a reversible cardiomyopathy in 2% to 7% of patients undergoing treatment. Antiangiogenic drugs such as sunitinib can also cause cardiotoxicity and uncontrolled hypertension.

2. **Alcohol** consumption is thought to represent a common cause of toxin-mediated cardiomyopathy; however, there is limited observational data on the actual incidence of the cardiomyopathy or the volume of alcohol consumption necessary to induce it. Total abstinence from alcohol may result in complete resolution, whereas continued use is associated with a 3- to 6-year mortality exceeding 50%.
3. **Stimulant drugs** including cocaine and methamphetamine may result in the development of heart failure via multiple derangements including progressive concentric hypertrophy and recurrent myocardial infarction.
4. **Toxin exposures** including lead, arsenic, and cobalt can result in progressive myocardial dysfunction.
- E. **Inflammatory cardiomyopathy** (i.e., myocarditis) is discussed in detail in Chapter 11.
- F. **Tachyarrhythmia-induced cardiomyopathy** can complicate the course of atrial fibrillation, atrial flutter, ectopic atrial tachycardia, and even occult sustained ventricular tachycardia and frequent premature ventricular contractions (> 20% to 30% of beats). In general, it is thought that persistent tachycardia in excess of 110 bpm is required to induce LV dysfunction. This is a critical diagnosis to make, as treatment of the underlying tachyarrhythmia generally results in complete resolution of the cardiomyopathy.
- G. **Peripartum cardiomyopathy** is defined as a dilated cardiomyopathy occurring between the last month of pregnancy and up to 5 months postpartum. The majority of peripartum cardiomyopathy patients improve with standard heart failure pharmacotherapy, with over 50% of patients experiencing complete normalization of cardiac function.
- H. **Valvular disorders** are common causes of heart failure. Aortic regurgitation and mitral regurgitation (MR) result in chronic volume overload and ultimately culminate in dilated cardiomyopathy. Severe aortic stenosis and outflow tract obstruction commonly lead to progressive LV dysfunction (see Chapters 14 and 15). Surgical correction is the preferred management of severe valvular lesions.
- I. **Miscellaneous disorders**
 1. **Thyroid disorders**
 - a. **Hypothyroidism** is common in patients with heart failure. Severe hypothyroidism (i.e., myxedema) may cause decreased cardiac output and heart failure. Bradycardia and pericardial effusion can develop in extreme cases of hypothyroidism.
 - b. Heart failure may complicate **hyperthyroidism**, especially in elderly patients with low ventricular reserve. Atrial fibrillation is a common accompanying arrhythmia, occurring in 9% to 22% of patients with thyrotoxicosis. Non-specific symptoms such as fatigue, weight loss, and insomnia predominate. Previously stable angina may become unstable. Patients treated with amiodarone may develop a wide range of thyroid disorders ranging from abnormal thyroid function tests to overt amiodarone-induced thyrotoxicosis or hypothyroidism. Both conditions can occur in otherwise normal thyroid glands.
 2. **Thiamine deficiency (beriberi)**. Although rare in industrialized countries, thiamine deficiency is still prevalent in the developing world. It can also occur in alcoholics or individuals observing fad diets. Wet beriberi includes features of **high-output cardiac failure such as marked edema, peripheral vasodilation, and pulmonary congestion**. The signs and symptoms of dry beriberi include glossitis, hyperkeratosis, and peripheral neuropathy. The laboratory diagnosis is made using decreased RBC transketolase and 24-hour urine thiamine

levels. Severe cases can present with lactic acidosis. Intravenous therapy with 100 mg of thiamine followed by daily oral supplementation can result in dramatic clinical improvement. Chronic use of high-dose diuretics may be complicated by subclinical thiamine deficiency of unknown significance.

3. **Other nutritional deficiencies.** Carnitine and selenium deficiency may result in dilated cardiomyopathy complicating chronic parenteral nutrition.
4. **High-output heart failure from anemia.** Acute anemia caused by rapid blood loss is associated with decreased cardiac output due by hypovolemic shock. In contrast, chronic anemia can be associated with symptoms of heart failure due to compensatory mechanisms. These include fluid retention, increased cardiac output, decreased vascular resistance, and increased 2,3-diphosphoglycerate with a resultant rightward shift in the oxyhemoglobin dissociation curve. Moderate degrees of chronic anemia (hemoglobin < 9 g/dL) typically only result in heart failure symptoms in patients with preexisting cardiac disease. Chronic anemia of severe proportions (hemoglobin < 7 g/dL) may result in high-output heart failure even in individuals with normal hearts. Evaluation and management of the underlying cause and supportive care are advised. Thresholds for transfusion depend on the clinical context and rapidity of blood loss. Iron repletion should be considered in iron-deficient patients and in inpatients is most readily achieved with the daily administration of intravenous ferric gluconate 125 mg for 8 to 10 days.
5. While early in its course **hemochromatosis** may present with restrictive cardiomyopathy, it typically progresses to a mixed or dilated form. Treatment with chelating agents or phlebotomy may improve cardiac function in both primary and secondary forms.
6. **Inherited myopathies** such as Becker's and Duchenne's muscular dystrophies, limb girdle dystrophy, and myotonic dystrophy are associated with dilated cardiomyopathy. Friedreich's ataxia is most commonly associated with hypertrophic cardiomyopathy, but in rare instances can present with a dilated phenotype. Mitochondrial cardiomyopathies may also present with dilated cardiomyopathy.
7. **Cardiac sarcoidosis** can present with LV dysfunction with regional hypokinesis or aneurysmal dilatation. It is frequently associated with conduction abnormalities and ventricular tachyarrhythmias. The diagnosis can be supported with stereotypical findings on cardiac MRI and positron emission tomography (PET). The diagnosis is rare in the absence of extracardiac manifestations.
8. **Chagas disease** caused by the flagellate protozoan *Trypanosoma cruzi* remains a common cause of heart failure in patients from Latin America. In the chronic symptomatic phase, patients typically present with a syndrome of ventricular dysfunction with regional wall motion abnormalities in the absence of obstructive coronary artery disease. This pattern should prompt *T. cruzi* titers in patients from endemic regions.

V. SIGNS AND SYMPTOMS

- A. **There is a wide spectrum of signs and symptoms in heart failure patients.** Subjective changes in signs and symptoms are often difficult to elicit and frequently leave insufficient time lag for therapeutic interventions prior to hospitalization.
 1. The most common and earliest presenting symptom is **dyspnea**, typically with exertion. **Orthopnea** is typical with more advanced disease. It is amongst the most sensitive (90%) and specific (90%) signs of decompensated heart failure. As further decompensation occurs, **paroxysmal nocturnal dyspnea** and **Cheyne-Stokes respiratory patterns** may occur.
 2. **Fatigue** and **exercise intolerance** are common complaints in patients with heart failure and may reflect diminished cardiac output. Seldom considered but highly prevalent symptoms include **nocturnal cough**, **insomnia**, and **depressed mood**.

3. **Palpitations** and **syncope** may occur in patients with underlying arrhythmia and require prompt evaluation.
 4. **Anorexia** and **abdominal pain** are common in advanced right heart failure.
- B. Physical examination** of patients with significant but well-compensated systolic heart failure may reveal no abnormalities. Physical signs vary according to the degree of compensation, the chronicity, and the chamber involvement.
1. **Volume overload** is the hallmark of heart failure. Typical signs of volume overload include the following:
 - a. **Weight gain** is a sensitive indicator of congestion.
 - b. **Pulmonary rales** due to accumulation of fluid in the pulmonary interstitium and alveoli secondary to high left atrial pressure are commonly referred to as **acute cardiogenic pulmonary edema**. Importantly, rales may be absent in patients with chronic systolic heart failure who develop compensatory perivascular and lymphatic changes.
 - c. **Jugular venous distention or elevated jugular venous pressure (JVP)** while not directly reflecting left-sided filling pressures can track these with a reasonable sensitivity (70%) and specificity (79%). JVP should be assessed at a 45° incline with the neck fully exposed. In cases of extreme JVP elevation, the patient may need to be seated upright in order to properly visualize. Five centimeters of water should be added to the vertical distance from the sternal angle to the meniscus of the JVP to account for the distance to the midpoint of the right atrium. Compression of the right upper quadrant and a resultant positive **hepatojugular reflex** (defined as a sustained increase in JVP of ≥ 4 cm) increase the sensitivity of the JVP for detecting congestion.
 - d. **Pedal edema** by some estimates is only present in 30% of patients with decompensated heart failure and is somewhat nonspecific, as it may reflect venous insufficiency, nephrotic syndrome, cirrhosis, or concomitant treatment with calcium channel blockers or thiazolidinediones.
 - e. **Ascites and hepatomegaly** may occur. When accompanied by a palpably pulsatile liver, hepatomegaly suggests severe tricuspid regurgitation.
 - f. A holosystolic murmur of **MR** is often present in the setting of LV dilatation.
 - g. **A third heart sound (S_3 gallop)** is best heard with the bell of the stethoscope in the left lateral position and signifies increased LV end-diastolic pressure.
 2. Often neglected are the subtle signs of **peripheral hypoperfusion**.
 - a. **Pulsus alternans** or a low-amplitude pulse in the absence of alternative explanations reflects severely impaired cardiac output.
 - b. Tachycardia and narrow pulse pressure also suggest diminished cardiac output.
 - c. Lethargy, pallor, mottled skin, cool extremities, and poor capillary refill are typical signs.
 - d. **Hypotension** itself may be one of the most important clinical findings in heart failure. Several studies have demonstrated that a systolic blood pressure < 90 mm Hg is a strong predictor of morbidity and mortality.

VI. DIAGNOSTIC EVALUATION

- A. Laboratory work** is used to diagnose potentially reversible causes, identify comorbidities, monitor and correct abnormalities before or during treatment, and assess the disease severity.
1. A **comprehensive metabolic panel** should be assessed on initial evaluation and then subsequently based on clinical judgment. Particular attention should be paid to the presence of hyponatremia, which portends a worse prognosis. Hypokalemia is common in the setting of ongoing diuretic therapy. Hyperkalemia can be seen in the context of overaggressive potassium repletion and ongoing treatment with ACE or aldosterone inhibitors or in diabetic patients with

associated type IV renal tubular acidosis. Aside from the pragmatic considerations, many real-world registries have identified elevated blood urea nitrogen (BUN) and creatinine as powerful predictors of outcome. Renal function must also be taken into account when considering therapy with renally excreted drugs. Transaminitis and in some cases a cholestatic pattern of liver function test abnormalities may be seen in the context of right heart failure.

2. **Anemia** is present in up to 40% of heart failure patients and is associated with increased mortality and functional impairment. While frequently due to anemia of chronic disease, a thorough diagnostic evaluation should be performed.
 3. The natriuretic peptides **B-type natriuretic peptide (BNP) and N-terminal pro-B-type natriuretic peptide (NT-proBNP)** are released in the setting of increased ventricular dilation or wall stress. Normal ranges (BNP < 100 pg/mL; NT-proBNP < 125 pg/mL if age < 75 years and < 450 pg/mL if age ≥ 75 years) must be interpreted in the context of associated conditions known to alter levels. Increasing age and worsening renal function are associated with increased levels. There is an inverse relationship between natriuretic peptides and body mass index.
 - a. **Screening for heart failure.** Although cardiac dysfunction has been associated with elevated natriuretic peptide levels, the sensitivity is relatively low in asymptomatic patients and is highly dependent on the cut-off levels chosen. In general, routine assessment of BNP is not recommended as a screening test for structural heart disease in asymptomatic patients.
 - b. **Diagnosing heart failure.** The primary use of natriuretic peptides remains the diagnosis of heart failure in symptomatic patients particularly when the diagnosis is unclear. The high negative predictive value (up to 90%) in this setting allows BNP testing to be useful to rule out a cardiac cause of symptoms. With the growing epidemic of obesity, it is important to remember that *normal natriuretic peptide levels may be present in morbidly obese patients with decompensated heart failure.*
 - c. **Management of heart failure.** While still controversial, there is emerging evidence that serial measurements of natriuretic peptides may be beneficial in guiding outpatient heart failure management and may result in decreased heart failure–related mortality versus usual care.
 - d. **Determining prognosis of heart failure.** Data now suggest that natriuretic peptide levels are closely correlated with morbidity and mortality in patients with both established heart failure and other cardiovascular diagnoses (e.g., stable coronary artery disease, acute coronary syndromes, pulmonary hypertension, and atrial fibrillation).
 4. **Other biomarkers.** A growing list of biomarkers assessing systemic inflammation, oxidative stress, extracellular matrix remodeling, and myocyte injury is commercially available or in development. While some of these provide useful prognostic information, it is not clear how to best integrate them into the diagnosis and management of heart failure.
 5. **Thyroid function testing** is warranted for all patients with a new diagnosis of heart failure.
 6. Iron studies including ferritin, serum iron, and total iron binding capacity (with calculation of percent transferrin saturation) should be performed to screen for hemochromatosis and occult iron deficiency.
 7. Standard laboratory screening for **modifiable cardiovascular risk factors** including fasting lipid panel and serum glucose should be obtained.
- B. The electrocardiogram (ECG)** may provide important information pertaining to the cause and management of heart failure and is a recommended component of the evaluation of any patient with a clinical diagnosis of heart failure.
1. It is important to look for evidence of prior myocardial infarction, chamber enlargement and hypertrophy, conduction disease, and supraventricular or ventricular arrhythmias.

2. Specific diagnoses can be suggested in the ECG. Cardiac amyloidosis classically presents with low voltages and a pseudoinfarction pattern in the anterior leads in stark contrast to echocardiographically thickened walls. Arrhythmogenic right ventricular (RV) cardiomyopathy may present with epsilon waves or localized prolongation (> 110 milliseconds) of the QRS complex in the right precordial leads.
 3. The ECG is an important means of assessing **dyssynchrony**. Marked first-degree atrioventricular (AV) block or very short AV delays in the presence of paced rhythms may contribute to AV dyssynchrony. The presence of QRS prolongation > 120 milliseconds (particularly left bundle branch block morphologies with QRS > 130 milliseconds) suggests interventricular dyssynchrony and remains the most important predictor of response to cardiac resynchronization therapy.
 4. **Holter or event monitors** are often useful in identifying occult arrhythmia and arrhythmia burden.
- C. Examination of the **chest radiograph** should include an assessment of the heart size and the condition of the pulmonary parenchyma. Determinations of cardiac size are best restricted to standard posteroanterior projections, as “portable” anteroposterior projections will magnify the cardiac silhouette. Lateral projections are useful to assess for RV enlargement, with associated filling of the retrosternal space. A normal cardiac silhouette does not exclude systolic or diastolic dysfunction. The lung field abnormalities may range from mild engorgement of the perihilar vessels to bilateral pleural effusions, Kerley B lines, and frank pulmonary edema.
- D. **Echocardiography** is perhaps the most useful diagnostic test in the evaluation of patients with heart failure. It can provide useful information pertaining to the etiology and prognosis of heart failure. As described in later sections, echocardiography also plays a key role in guiding heart failure therapy.
1. **Etiology of heart failure.** Regional wall motion abnormalities occurring in an anatomic coronary artery distribution are suggestive of ischemic cardiomyopathy. However, regional wall motion abnormalities can also be seen in the context of nonischemic dilated cardiomyopathy, stress-induced cardiomyopathy, and infiltrative cardiomyopathies (with inferobasal wall motion abnormalities classically seen in the setting of cardiac sarcoidosis). The presence and severity of valvular stenosis or insufficiency can be assessed as can the relative dysfunction of the right and left ventricles.
 2. **Prognosis in heart failure.** The following parameters are useful in assessing the risk of heart failure–associated morbidity and mortality.
 - a. **EF and LV dimensions.** While correlating poorly with heart failure symptoms, exercise capacity, and oxygen consumption, the EF provides valuable prognostic information with morbidity and mortality closely linked to EF and LV volumes. The American Society of Echocardiography recommends that assessment of EF and LV volumes be made using the biplane Simpson’s method of disks.
 - b. **LV mass.** Remodeling in the failing heart results in increased LV mass due to eccentric hypertrophy, which worsens prognosis. Eccentric hypertrophy is defined echocardiographically as an LV mass > 95 g/m² in women and > 115 g/m² in men with a regional wall thickness ($2 \times$ posterior wall thickness/LV end-diastolic dimension) of ≤ 0.42 .
 - c. **The myocardial performance index (Tei index).** The Tei index provides a useful assessment of systolic and diastolic function and is equal to (the isovolumic contraction time + the isovolumic relaxation time)/the ejection time. All dimensions are obtained via pulse wave or tissue Doppler. A Tei index of > 0.77 in patients with dilated cardiomyopathy is highly predictive of cardiovascular morbidity and mortality.
 - d. **Measures of diastolic dysfunction.** Many of the measures of diastolic dysfunction detailed in Chapter 9 have powerful prognostic ability in patients

with systolic heart failure. The presence of a restrictive filling pattern ($E/A > 2$, deceleration time < 115 to 150 milliseconds) persisting despite Valsalva maneuver is a particularly ominous finding.

E. Other imaging modalities

1. **Cardiac magnetic resonance (CMR) imaging** (Chapter 51). CMR offers unparalleled myocardial tissue characterization and allows for myocardial viability assessment. As such, it is an increasingly useful tool in the diagnosis of specific cardiomyopathies (e.g., LV noncompaction and cardiac sarcoidosis). The distribution of late gadolinium hyperenhancement representing scar can effectively discriminate between ischemic and nonischemic causes of fibrosis. Cine MRI provides accurate assessments of chamber volumes and LV and RV systolic function that can be performed in arbitrary tomographic views. Major limitations are incompatibility with most implanted electronic cardiovascular devices and the potential for nephrogenic sclerosing fibrosis with the use of gadolinium-based contrast agents in patients with preexisting renal insufficiency (see Chapter 51).
2. **Nuclear imaging.** Single photon emission computed tomography (SPECT) and PET imaging are primarily of use in ruling out myocardial ischemia and/or viability. **Viability assessment** (i.e., discriminating between scarred and hibernating myocardium) is critical in the assessment of patients with heart failure and coronary artery disease and the potential for myocardial recovery with revascularization. This can be achieved with PET using concomitant flow and metabolism tracers (typically [^{18}F]fluorodeoxyglucose) or thallium 201 SPECT redistribution imaging (see Chapter 50). There is growing evidence that PET is superior to SPECT in patients with systolic dysfunction, and when available it should be used preferentially in patients with an LVEF $< 35\%$. Dobutamine stress echocardiography and CMR are alternative means of assessing viability. Radionuclide ventriculography using multiple-gated acquisition scanning has long served as the gold standard for precise serial measurements of the LVEF (classically in the evaluation of patients receiving cardiotoxic chemotherapeutics). Increasingly, however, it is being surpassed by CMR and three-dimensional echocardiography.

F. Right heart catheterization (see Chapter 60). Invasive hemodynamic monitoring is often helpful in the diagnosis and inpatient management of heart failure. Right heart catheterization can be combined with exercise testing or infusions of inotropic or vasodilatory agents to study their hemodynamic effects. Reasonable indications for right heart catheterization include short-term management of acute cardiogenic shock, evaluation of patients for cardiac transplantation or mechanical circulatory support, clarification of hemodynamics in the context-specific comorbidities (e.g., suspected RV infarction or mechanical complications of myocardial infarction), adjustment of therapy in patients with recurrent or refractory symptoms, and optimization of medical therapy in order to facilitate weaning from inotropes.

1. **Cardiac output/index** is one of the important measurements provided by right heart catheterization. It can be determined using the thermodilution technique or the Fick method using an estimated or derived oxygen consumption and a directly measured mixed venous oxygen saturation (MVO_2).
2. **Pulmonary capillary wedge pressure (PCWP)** should be measured in all cases. An inability to normalize the PCWP (< 16 mm Hg) with pharmacotherapy was shown in the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial to confer a twofold increased risk of mortality.
3. **Right atrial pressure** is an important indicator of volume status and right heart function. An elevated central venous pressure has been shown to be the most important predictor of worsening renal function during hospitalizations for acute decompensated heart failure.

G. Coronary angiography (see Chapter 64). There are many approaches to determining which patients with systolic heart failure warrant evaluation by coronary angiography. The Heart Failure Society of America recommends performing coronary angiography in patients with a high pretest probability of underlying ischemic cardiomyopathy and who are candidates for percutaneous or surgical revascularization. At a minimum, patients meeting this description should undergo some form of noninvasive stress testing. Some centers advocate for a baseline coronary angiogram in all patients with newly established systolic heart failure regardless of risk factors or presentation.

H. Endomyocardial biopsy (see Chapter 61) is indicated only when a specific primary myocardial disease is suspected and other causes of decompensation have been ruled out. A recent AHA/ACC/ESC writing group identified 14 clinical scenarios in which there is an incremental diagnostic, prognostic (e.g., amyloidosis), or therapeutic (e.g., giant cell myocarditis) value to biopsy that can be weighed against the procedural risk.

I. Cardiopulmonary exercise testing (metabolic stress testing) while not recommended as part of the routine evaluation of patients with heart failure should be considered in the context of symptoms out of proportion with objective measures of disease severity, discriminating between cardiac and pulmonary etiologies of dyspnea, or assessing candidacy for cardiac transplantation or mechanical circulatory support. Several routinely measured parameters are highly predictive of prognosis in patients with established heart failure.

1. Peak oxygen consumption (Vo_2) is perhaps the most important parameter in objectively describing functional capacity and prognosticating. Normal values based on age and sex are indexed to body weight, with a normal value being $> 84\%$ predicted. Patients being considered for heart transplantation undergo risk stratification with a metabolic stress test. Patients with a peak $\text{Vo}_2 < 14 \text{ mL/kg/min}$ or $< 50\%$ predicted are at increased risk for adverse cardiovascular events and if the limitation is deemed to be cardiac should be considered for transplantation. Interpretation of the peak Vo_2 is highly dependent on the adequacy of effort as assessed by the respiratory exchange ratio (RER). The RER is the ratio of VCO_2/Vo_2 and is at steady state an estimate of the respiratory quotient. It signifies the conversion to anaerobic metabolism and the sudden rise in CO_2 production occurring with the onset of metabolic acidosis. Failure to achieve an $\text{RER} > 1.05$ suggests insufficient effort or premature termination of the study. Up to 50% of heart failure patients are incapable of achieving an adequate RER, with a modified Bruce treadmill protocol necessitating the use of alternative protocols.

2. Ventilatory anaerobic threshold is another means of assessing the adequacy of effort and represents the point at which minute ventilation (V_E) increases out of proportion with Vo_2 (typically occurring at 60% to 70% of peak Vo_2).

3. V_E/VCO_2 slope is a dimensionless ratio indicating the relationship between minute ventilation and CO_2 production. The slope is elevated in most patients with heart failure and is inversely related to cardiac output at peak exercise. A slope > 35 identifies higher risk individuals independently of peak Vo_2 .

J. Sleep study. Obstructive sleep apnea and central sleep apnea are common comorbidities contributing adversely to the pathogenesis and prognosis of patients with heart failure. There should be a low threshold for appropriate testing.

VII. TREATMENT. The effective management of heart failure relies on appreciating the distinction between acute and chronic therapies.

A. Acute heart failure syndromes. In the United States, AHFS continue to constitute the most common indication for hospital admission in adults over age 65 years. These hospitalizations represent an inflection point in the course and prognosis of the chronic disease, with 90-day and 1-year postdischarge mortality as high as 14%

TABLE 8.3 Precipitants of Acute Decompensated Heart Failure

Medication nonadherence
Myocardial ischemia, infarction
Arrhythmias (tachyarrhythmias, bradycardia)
Infection
Anemia
Alcohol consumption
Pregnancy
Worsening hypertension
Acute valvular insufficiency
Drugs that can acutely worsen HF symptoms
Calcium channel antagonists
β -Blockers
Nonsteroidal anti-inflammatory drugs
Thiazolidinediones
Antiarrhythmic agents (all class I agents, sotalol)

and 37%, respectively. Only 20% of AHFS represent patients with de novo heart failure. The majority are patients with worsening chronic heart failure. The initial management goals include symptom improvement, decongestion, and hemodynamic stabilization with optimization of tissue perfusion. It is important to attempt to identify and correct any precipitating factors (Table 8.3).

1. Invasive hemodynamic monitoring

a. **Pulmonary artery catheter.** The **ESCAPE** trial demonstrated that the routine use of a pulmonary artery catheter in the management of patients with AHFS did not result in a reduction in subsequent hospitalizations or mortality but did result in an increase in anticipated complications. The use of a pulmonary artery catheter should therefore be restricted to the scenarios detailed above where there is need for clarification of cardiac indices or filling pressures and in critically ill patients failing to respond to standard therapies. When available, a PCWP of > 18 mm Hg suggests cardiogenic pulmonary edema and a cardiac index of < 2.0 L/min/m² is consistent with cardiogenic shock.

b. **Arterial catheter.** Continuous blood pressure monitoring with an arterial catheter can be useful in cases with marginal blood pressure and allows for optimal titration of intravenous vasodilators.

2. **Maximizing oxygenation** is vital. All patients with acute cardiogenic pulmonary edema should be positioned upright and receive supplemental oxygen. **Noninvasive positive pressure ventilation (NIPPV)** should be considered in those with ongoing increased work of breathing, respiratory acidosis, or persistent hypoxemia. The Noninvasive Ventilation in Acute Cardiogenic Pulmonary Edema (**3CPOE**) trial demonstrated that NIPPV results in more rapid resolution of symptoms and metabolic derangements than continuous positive airway pressure (CPAP) ventilation or standard oxygen therapy. While there was no evidence of a reduction in short-term mortality, this can be an invaluable tool

often forestalling intubation. Patients who fail to respond to NIPPV should be promptly intubated. The use of positive end-expiratory pressure (PEEP) can be effective in improving oxygenation, but high levels of PEEP come at the cost of reduced systemic venous return and cardiac output, which may be problematic in patients in shock.

3. **Vasodilators.** In the absence of symptomatic hypotension, intravenous vasodilators are the first-line therapy for the management of cardiogenic pulmonary edema.
 - a. **Nitroglycerin** reduces LV filling pressures via venodilation and to a lesser extent via systemic afterload reduction. It may be given rapidly in the emergency setting (0.4 to 0.8 mg, given sublingually every 3 to 5 minutes) and by means of intravenous infusion in the subacute setting (starting dosage of 0.2 to 0.4 $\mu\text{g}/\text{kg}/\text{min}$), with titration every 5 minutes on the basis of symptoms or mean arterial pressure (MAP). While there is no maximal dose, increasing beyond 300 to 400 $\mu\text{g}/\text{min}$ likely yields no additional benefit and should prompt the addition of another vasodilator. Tachyphylaxis can occur with high-dose infusions. Headache is the most common side effect, and use is contraindicated in the setting of recent use of phosphodiesterase-5 (PDE-5) inhibitors.
 - c. **Sodium nitroprusside** is a potent vasodilator with balanced venous and arteriolar effects. It requires careful hemodynamic monitoring (typically by arterial line). A starting dosage of 0.1 to 0.2 $\mu\text{g}/\text{kg}/\text{min}$ is used and titrated every 5 minutes to achieve a clinical response while maintaining an MAP > 65 mm Hg. Nitroprusside is particularly useful in instances where a rapid and large reduction in afterload is desired (e.g., cardiogenic shock and acute severe aortic regurgitation or MR). While cyanide and thiocyanate toxicity is exceedingly rare with short durations of therapy, nitroprusside should be used with caution in patients with severe renal dysfunction. Long-term, high-dose infusions should be avoided. In patients with myocardial ischemia, nitroglycerin or a combination of nitroglycerin and nitroprusside is preferred to avoid the theoretical risk of coronary steal.
 - d. **Nesiritide** is an intravenous vasodilator that gained popularity in the acute care setting because of its ease of use in the absence of invasive hemodynamic monitoring. Typical dosing starts with 2 mg/kg delivered by intravenous bolus followed by an infusion at a rate of 0.01 mg/kg/min for up to 48 hours. The recently published Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure (**ASCEND-HF**) trial demonstrated that nesiritide had no effect on death or rehospitalization for heart failure at 30 days when compared with conventional therapy. While providing some reassurance regarding previous safety concerns, these results have led most experts to discourage its use on the basis of lack of efficacy.
4. **Diuretics.** In addition to their ability to gradually reduce intravascular volume, diuretics have an immediate vasodilatory effect, which may be responsible for their prompt symptom relief. Reductions in filling pressures may be associated with augmented forward flow due to optimization of LV and RV mechanics and interventricular interaction. Because many patients with acute cardiogenic pulmonary edema do not have total body salt and water excess, the judicious use of diuretics is recommended. Often, filling pressures normalize with the use of vasodilators alone. Patients without chronic exposure to loop diuretics usually respond to 20 to 40 mg of intravenous furosemide. Patients undergoing long-term furosemide therapy typically need an intravenous bolus dose at least equivalent to their oral dose. Rather than an arbitrary therapeutic goal of net fluid balance or an estimated dry weight, frequent clinical assessments of volume status should

guide therapy and define the point at which conversion to an oral maintenance regimen should occur. Nevertheless, up to 30% of patients with AHFS continue to have symptoms of congestion at the time of discharge. Important adverse effects include hypotension, hypokalemia, hypomagnesemia, and hypocalcemia. There is also extensive evidence suggesting that intravenous diuretics may result in at least transient neurohormonal activation which is theoretically disadvantageous. Electrolyte repletion is best achieved with scheduled doses of potassium and magnesium supplements to prevent severe deficits. Results of the recently published Diuretic Optimization Strategies Evaluation (**DOSE**) trial demonstrate no benefit of continuous or bolus dose intravenous diuretic administration and no detriment from high doses (an intravenous dose 2.5 times the patients' chronic oral dose of furosemide). If a continuous diuretic infusion is opted for, it should be preceded by a bolus dose, as should any subsequent titration in the continuous rate. Diuretic resistance can be addressed with escalating doses of loop diuretics and subsequently with the addition of a thiazide diuretic (hydrochlorothiazide, metolazone, or chlorothiazide). Some degree of worsening renal function must often be tolerated in order to achieve adequate decongestion. However, if progressive renal failure occurs despite persistent congestion, ultrafiltration or the addition of an intravenous vasodilator or inotrope needs to be considered.

5. **Inotropic therapy.** When signs and symptoms of decompensated heart failure persist despite administration of vasodilators and diuretics, intravenous inotropes may be considered. Their use should be restricted to patients with clear clinical or direct hemodynamic evidence of refractory elevated filling pressures and reduced cardiac output. For patients without significant hypotension, the intravenous inodilators dobutamine or milrinone can be used to augment cardiac output. Both drugs are associated with increased myocardial oxygen demand and cardiac arrhythmias and should be used with extreme caution in patients with ischemia and preexisting arrhythmias. Both drugs may cause hypotension, although this is more common with loading doses of milrinone. *There is no evidence to support benefit with the use of chronic or intermittent infusion of inotropic agents, and in fact, there is extensive observational data suggesting a trend toward increased postdischarge mortality.* Use is typically confined to the acute care setting and as a bridge to transplant/mechanical circulatory support or palliation in patients who are not candidates for advanced therapies. In cases of severe hypotension (especially as a result of administration of vasodilators or β -blockers), temporary use of vasopressors such as dopamine, norepinephrine, and phenylephrine may be necessary. In contrast to the conventional wisdom, recent prospective data suggest that norepinephrine is not inferior to dopamine in the setting of cardiogenic shock.
 - a. **Dobutamine** acts on β -1 and to a lesser extent on β -2 and α -1 adrenergic receptors. It has a shorter half-life than milrinone and usually is the drug of choice in the acute setting. Infusions are usually started at 2.5 to 5.0 $\mu\text{g}/\text{kg}/\text{min}$. On the basis of hemodynamic response, it may be titrated by 1 to 2 $\mu\text{g}/\text{kg}/\text{min}$ every 30 minutes until the desired effect or a dosage of 10 $\mu\text{g}/\text{kg}/\text{min}$ is reached.
 - b. **Milrinone** is a PDE inhibitor that increases myocardial inotropy by inhibiting the degradation of cyclic adenosine monophosphate. It is a potent systemic and pulmonary vasodilator due to its effects on vascular PDE. For patients who need an immediate inotropic response, a loading dose of 50 $\mu\text{g}/\text{kg}$ over 10 minutes is followed by an infusion of 0.125 to 0.75 $\mu\text{g}/\text{kg}/\text{min}$. Because it does not target β -receptors, milrinone may be more effective than dobutamine in the setting of recent or ongoing β -blocker therapy.
6. **Ultrafiltration** has been used as an alternative to pharmacologic diuresis in acute decompensated heart failure. The Ultrafiltration vs. Intravenous Diuretics

for patients hospitalized for Acute Decompensated Congestive Heart Failure (**UNLOAD**) study demonstrated that ultrafiltration was safe and resulted in a reduced need for intravenous diuretics and inotropes. Whether ultrafiltration should be considered a first-line alternative to standard intravenous diuretics will depend on the outcome of future trials assessing the relative safety, efficacy, and cost-effectiveness. Currently the use of ultrafiltration is reserved for patients refractory to intravenous diuretic therapy or with diuresis complicated by worsening renal function.

7. **Vasopressin antagonists.** The oral vasopressin receptor 2 antagonist tolvaptan was shown to be safe and results in short-term symptom improvement in patients hospitalized with acute decompensated heart failure in the Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan (**EVEREST**) trial. This occurred without a reduction in long-term heart failure morbidity or mortality. Tolvaptan and the nonselective intravenous vasopressin receptor inhibitor conivaptan are both approved for the management of hypervolemic or euvolemic hyponatremia that can accompany decompensated heart failure.
 8. **Temporary mechanical circulatory support.** The use of temporary and permanent mechanical circulatory support is described in detail in Chapter 12. Patients with refractory cardiogenic shock and cardiogenic pulmonary edema may benefit from the temporary use of intraaortic balloon counterpulsation or an alternative temporary means of mechanical circulatory support (i.e., venoarterial extracorporeal membrane oxygenation, Impella, or TandemHeart) may facilitate bridging to stabilization or further decision making.
 9. Diagnosis and management of atrial and ventricular tachyarrhythmias is critical to the care of patients with acute decompensated heart failure, as these frequently precipitate exacerbations and alter the disease course. Their management is discussed in detail in Chapter 21.
 10. **Transition to chronic pharmacotherapy** is implemented once clinical stability is achieved. Generally, vasodilators (ACE inhibitors, angiotensin II receptor blockers [ARBs], or hydralazine/isosorbide dinitrate) are reintroduced first in concert with weaning of intravenous vasodilators. If β -blockers were held due to cardiogenic shock, they can be cautiously reintroduced in stable, euvolemic patients.
- B. Chronic medical therapies.** The goals of chronic medical therapy are to prolong survival and to improve symptoms and functional status. While there have been few recent major advancements in pharmacotherapy, the evolution of therapies with profound survival benefit for patients with heart failure represents a triumph of modern medicine.
1. **ACE inhibitors** have been shown to reduce morbidity and mortality among patients with systolic heart failure. The mechanism of long-term benefit is related to attenuation of the RAS. In addition, ACE inhibitors improve symptoms, clinical status, and exercise capacity.
 - a. **Use of an ACE inhibitor is the first-line therapy for asymptomatic and symptomatic LV dysfunction.** The dose of the ACE inhibitor should be increased to the target doses demonstrating clinical benefits in trials (Table 8.4). Although there are theoretical benefits of using “tissue” ACE inhibitors (e.g., quinapril and ramipril), there are no data to support their preferential use. Relative contraindications include hyperkalemia (potassium > 5.5 mEq/L), renal insufficiency (creatinine > 3.0 mg/dL), and hypotension (systolic blood pressure < 90 mm Hg) and should be gauged on a case-by-case basis. It is not advisable to stop ACE inhibitors in patients with systolic heart failure, even when there is complete resolution of symptoms.

TABLE 8.4 Drug Dosing for Common Medical Therapies for Chronic Heart Failure

Drug	Start (mg)	Target (mg)	Max (mg)
ACE inhibitors			
Captopril (Capoten)	6.25–12.5 tid	50 tid	100 tid
Enalapril (Vasotec)	2.5–5 bid	10 bid	20 bid
Lisinopril (Prinivil, Zestril)	2.5–5 qd	20 qd	40 qd
Ramipril (Altace)	1.25–2.5 bid	5 bid	10 bid
Quinapril (Accupril)	5 bid	20 bid	20 bid
Fosinopril (Monopril)	2.5 or 5 bid	20 bid	20 bid
Benazepril (Lotensin) ^a	2.5 or 5 bid	20 bid	20 bid
Moexipril (Univasc) ^a	7.5 qd	30 qd	30 qd
Trandolapril (Mavik)	1 qd	4 qd	4 qd
Angiotensin receptor blockers			
Candesartan (Atacand)	16 qd	32 qd	32 qd
Valsartan (Diovan)	80 qd	160 qd	320 qd
Losartan (Cozaar) ^a	12.5–25 qd	50 qd	100 qd
Irbesartan (Avapro) ^a	150 qd	300 qd	300 qd
Telmisartan (Micardis) ^a	40 qd	80 qd	80 qd
Hydralazine/isosorbide dinitrate			
Hydralazine	25 qid	50–75 qid	100 qid
Isosorbide dinitrate	10–20 tid	20–80 tid	80 tid
Hydralazine–isosorbide dinitrate (BiDil)	25/37.5 tid	50/75 tid	50/75 tid
Aldosterone antagonists			
Spironolactone (Aldactone)	12.5–25 qd	25 qd	50 bid
Eplerenone (Inspra)	25 qd	50 qd	100 qd
Diuretics^b			
Furosemide (Lasix)	10 qd (IV)	As required	1,000 qd (IV)
	20 qd (po)		240 bid (po)
Bumetanide (Bumex)	1 qd	As required	10 qd
Torsemide (Demadex)	10 qd	As required	200 qd
Ethacrynic acid (Edecrin)	50 qd	As required	200 bid
Hydrochlorothiazide (HCTZ)	25 qd	As required	50 qd
Triamterene (Maxzide)	50 qd	As required	100 bid
Metolazone (Zaroxolyn)	2.5 qd	As required	10 qd

TABLE 8.4	Drug Dosing for Common Medical Therapies for Chronic Heart Failure (<i>Continued</i>)
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Drug	Start (mg)	Target (mg)	Max (mg)
β-Blockers			
Carvedilol (Coreg)	3.125 bid	25 bid	50 bid
Carvedilol phosphate (Coreg CR)	10 qd	40 qd	80 qd
Metoprolol succinate (Toprol XL)	25 qd	150–200 qd	200 qd
Bisoprolol (Zebeta) ^a	1.25 qd	10 qd	20 qd

ACE, angiotensin-converting enzyme.

^aNot yet approved by the FDA for management of heart failure.

^bOral to IV conversion for furosemide is approximately 2:1. Oral to IV conversion for all other loop diuretics is 1:1.

- b. After initiation, close monitoring for **hyperkalemia** and **renal insufficiency** is warranted.
 - (1) **Hypotension** is common, especially with first dose in a volume-depleted patient (e.g., after aggressive diuresis). This may require downtitration of diuretic doses and other vasodilator therapy. Due to its short half-life, captopril is usually used in the acute setting (e.g., after myocardial infarction).
 - (2) **Renal insufficiency** and **hyperkalemia** may occur when ACE inhibitors are given in the setting of volume depletion. **It is crucial to discontinue other nephrotoxic agents (e.g., nonsteroidal anti-inflammatory agents)** and ensure adequate kidney perfusion. **If BUN or creatinine levels increase by < 50%, ACE inhibitors can be continued safely; if they increase by > 50%, the ACE inhibitor dose should be halved; if they increase by > 100%, the ACE inhibitor should be held and switched to hydralazine and isosorbide dinitrate.** In the case of hyperkalemia, discontinuation of potassium supplementation and reducing the ACE inhibitor dose is usually effective.
- c. Unique side effects of ACE inhibitors are cough and angioedema.
 - (1) The **cough** associated with ACE inhibitors is related to increased levels of bradykinin. It tends to be nonproductive and involuntary, rarely resolving with altering the dose or specific agent. All attempts should be made to identify an alternative cause of cough before discontinuing ACE inhibitors.
 - (2) **Angioedema** is a rare complication of ACE inhibitors (0.4%). It involves soft tissue edema of the lips, face, tongue, and, occasionally, the oropharynx and epiglottis. Angioedema typically begins within 2 weeks of initiation of ACE inhibitor therapy, but some patients present with this complication months to years after starting therapy. **Angioedema is an absolute contraindication to the use of any type of ACE inhibitor.**
- 2. **Angiotensin II receptor blockers** are specific receptor antagonists to the angiotensin II type 1 receptors. Although they theoretically provide more complete inhibition of the deleterious effects of angiotensin II than do ACE inhibitors, clinical trials have not demonstrated superiority in patients with heart failure. In general, ARBs are used and monitored in the same manner as ACE inhibitors. These drugs are reserved for patients who are ACE inhibitor intolerant, although in practice, they are used extensively. ARBs have a similar side-effect profile to ACE inhibitors (e.g., hypotension, renal insufficiency, and hyperkalemia). There appears to be a < 10% incidence of cross-reactivity for ACE inhibitor-associated

angioedema in patients receiving ARBs. However, consideration for the use of these agents must be weighed against the life-threatening nature of this complication. Whether ARBs can produce additional benefit when added to ACE inhibitors is still being debated. While the addition of an ARB is reasonable in patients on maximal medical therapy including target doses of ACE inhibitors and β -blockers with persistent symptoms, it is preferable to add an aldosterone antagonist in this setting. ARBs should not be added to an ACE inhibitor in the postmyocardial infarction period. Valsartan and candesartan are the best studied ARBs in patients with heart failure and should be used preferentially.

3. The combination of **hydralazine** and **isosorbide dinitrate** may provide a reduction in morbidity and mortality in selected heart failure patients. A fixed dose combination of hydralazine and isosorbide dinitrate (BiDil) demonstrated a substantial reduction in mortality when added to African American patients on optimal medical therapy including ACE inhibitors and β -blockers in the African-American Heart Failure Trial (A-HeFT). This combination is also indicated in patients intolerant of ACE inhibitors or ARBs. Side effects of hydralazine may include reflex tachycardia and rarely drug-induced lupus erythematosus.
4. **β -Adrenergic blockers (β -blockers).** Once considered to be contraindicated in patients with heart failure, β -blockers are now considered **first-line therapy for symptomatic patients with heart failure (NYHA class II, III, or stable class IV)** because of their consistent mortality benefits.
 - a. It is often customary to start ACE inhibitors before β -blockers. This in part reflects the fact that all major β -blocker trials demonstrated their benefit on a background of therapy with ACE inhibition. Furthermore, while ACE inhibitors provide immediate beneficial hemodynamic effects, β -blockers may acutely result in diminished LVEF and cardiac output, which may be poorly tolerated in decompensated patients. In some instances (e.g., postmyocardial infarction and comorbid tachyarrhythmias), β -blockers may be particularly beneficial and should be started before or concurrently with ACE inhibitors. β -Blockers should generally not be initiated or titrated in the setting of acutely decompensated heart failure whether due to congestion or severely impaired cardiac output.
 - b. Only carvedilol, bisoprolol, and metoprolol succinate have been approved for the medical treatment of chronic heart failure. Although atenolol and metoprolol tartrate are widely available and relatively inexpensive, there is no evidence to support their use in this population. β -Blockers with intrinsic sympathomimetic activity (pindolol and acebutolol) in particular should be avoided.
 - c. Relative contraindications to β -blocker therapy are a heart rate < 60 bpm, symptomatic hypotension, more than minimal pulmonary or systemic congestion, signs of peripheral hypoperfusion, a PR interval > 0.24 seconds, second- or third-degree AV block, a history of severe reactive airway disease, and peripheral arterial disease with resting limb ischemia. It is important to note that these are relative contraindications and particularly in the setting of reactive airway disease and peripheral arterial disease, the risks of β -blocker therapy must be weighed against their known benefits.
 - d. Current recommendations are to start β -blockers in those who are clinically euvolemic. The general principle is to “start low and go slow.” The initial dose is **slowly up-titrated every 2 to 4 weeks over 3 to 4 months to achieve target doses**, provided that the patient can tolerate side effects. It is imperative to maintain contact with the patient and adjust vasodilator or diuretic therapy during titration. It is not advisable to stop β -blockers in patients with a history of heart failure, even if there is complete resolution of symptoms and LV dysfunction.

- e. Every effort should be made to achieve target doses, but it is clear that even low doses of these drugs provide benefit. While the degree of β -blockade appears to be the best predictor of long-term response, there is no evidence to support titration to a given resting heart rate.
 - f. Side effects are common when using β -blockers. Patients should understand that these drugs are used to prolong survival and often do not improve symptoms.
 - (1) **Dizziness** and **light-headedness** are common and may be related to hypotension or heart block. **Significant bradycardia** mandates dose reduction of β -blockers and other rate-lowering agents such as digoxin and amiodarone. **Advanced heart block** is a contraindication to β -blockers unless a permanent pacemaker is present. **Hypotension** can be managed by staggering the timing of drug administration. In practice, carvedilol (with its nonselective, α_1 -blocking vasodilator effects) may have greater blood pressure lowering than selective β_1 agents such as metoprolol succinate. Both drugs are well tolerated in up to 70% of heart failure patients in our clinics.
 - (2) **Worsening heart failure** is still an important adverse effect of β -blockers. Intensification of diuretic therapy and dose reduction or slower titration may be necessary.
5. **Aldosterone receptor antagonists** have long been used as weak, potassium-sparing diuretics in patients with heart failure. The concept of incomplete blockade of the RAS by ACE inhibitors led to studies demonstrating significant pleiotropic effects of aldosterone antagonism in patients with advanced heart failure including antifibrotic effects and a reduction in sudden cardiac death. Results from the Randomized Aldactone Evaluation Study (**RALES**), Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (**EPHESUS**), and now Eplerenone in Patients with Systolic Heart Failure and Mild Symptoms (**EMPHASIS-HF**) trial have demonstrated substantial mortality benefit in all stages of heart failure.
- a. Aldosterone inhibitors are indicated in patients with NYHA class II symptoms and an LVEF $\leq 30\%$ or NYHA class III or IV patients with an LVEF $\leq 35\%$ already treated with ACE inhibitors and β -blockers and without significant renal dysfunction (creatinine > 2.5 mg/dL) or hyperkalemia (potassium > 5 mEq/L). Their use is also indicated in patients with postinfarction LV dysfunction (LVEF $\leq 40\%$) with any heart failure symptoms or diabetes mellitus.
 - b. In most cases, potassium supplementation should be reduced or discontinued. A basic metabolic panel should be checked within 1 week after initiation and monitored at regular intervals.
 - c. The most common and life-threatening side effect of aldosterone antagonists is **hyperkalemia**, which is particularly problematic in patients with concomitant **renal insufficiency** and diabetes mellitus (type IV renal tubular acidosis). **Painful gynecomastia** and **galactorrhea** may occur when using spironolactone.
 - d. While studies were typically performed with either spironolactone (RALES) or eplerenone (EPHESUS and EMPHASIS-HF), most experts believe that aldosterone inhibitors work via a class effect. Our approach is to initiate treatment with spironolactone due to its low cost and to transition to eplerenone only in the setting of significant gynecomastia.
6. **Diuretics** are used to maintain euvolemia and to improve symptoms, but their overuse can result in volume contraction, hypotension, and renal dysfunction.
- a. An effective and inexpensive initial regimen includes 20 to 120 mg of furosemide taken orally each day. If furosemide doses higher than 120 mg/d are

needed, a second evening dose is typically prescribed. If this regimen fails, a daily dose of a thiazide diuretic such as metolazone or hydrochlorothiazide can be added 30 minutes prior to furosemide dosing.

- b. More expensive loop diuretics (e.g., torsemide and bumetanide) may have superior bioavailability and may be more effective in diuretic-resistant patients. Torsemide in particular may have unique benefits in the form of antifibrotic effects and minimization of the postdiuretic sodium retention that complicates the use of loop diuretics with shorter half-lives.
 - c. The concept of **diuretic resistance** is evolving. Very often, this is contributed to by a failure to adhere to a low-sodium (< 2,000 mg/d) diet.
 - d. The goal of chronic diuretic therapy is maintenance of euvolemia. This is most reliably achieved in patients who record daily weights and make physician-supported changes in diuretic dosing on an as-needed basis.
7. **Digoxin** is reasonable to use in patients with persistent heart failure symptoms despite appropriate medical therapy including ACE inhibitors and β -blockers and in patients with atrial fibrillation to control ventricular rate.
 - a. Despite a fairly narrow therapeutic window, digoxin is safe and significantly reduces heart failure hospitalizations. A typical starting dose of 0.125 mg of digoxin daily is appropriate in patients with normal renal function.
 - b. While the **Digitalis Investigation Group (DIG) trial** demonstrated the best clinical outcomes in patients with a serum digoxin concentration of 0.5 to 0.8 ng/mL, routine measurement of levels is not recommended in the absence of concern for toxicity.
8. **Other drugs of importance.** **Statins** should be used in the secondary prevention of atherosclerotic cardiovascular disease without regard to the presence of heart failure. There is no evidence of benefit in heart failure patients without coronary artery disease. While **aspirin** clearly prevents reinfarction and other vascular events in patients with known coronary artery disease, there is growing evidence from observational and randomized studies that it may worsen outcomes in heart failure patients via inhibition of prostaglandin synthesis and the resultant adverse hemodynamic and renal effects. This remains a controversial subject and the decision of whether to use aspirin or not should be made on a case-by-case basis. It should likely be avoided in patients without coronary disease who have refractory heart failure symptoms.
9. **Electrolyte supplementation** is among the most important and least emphasized areas in chronic heart failure management. Potassium depletion is common with diuretic therapy, whereas hyperkalemia can be caused by ACE inhibitors, spironolactone, or worsening renal insufficiency. In general, oral potassium supplementation is necessary to maintain serum potassium level in the ideal range of 4.0 to 5.0 mEq/L. Magnesium, thiamine, and calcium depletion are also common with long-standing diuretic therapy.
10. **Device therapy.** Chapters 55 and 56 provide detailed coverage of the indications, contraindications, and clinical issues related to implantable cardioverter defibrillators (ICD) and cardiac resynchronization therapy (CRT-D).
11. **Device monitoring.** Currently implanted electrical cardiovascular devices including ICD and CRT-Ds have the capability to remotely monitor a variety of electrophysiologic (e.g., heart rate variability, atrial arrhythmia burden and rate, ventricular tachycardia, % biventricular pacing, and average heart rate) and physiologic (e.g., patient activity and intrathoracic impedance) parameters with prognostic value. Several implantable hemodynamic monitors are under development for use in patients with advanced heart failure. How to best integrate device monitoring into a comprehensive approach to heart failure disease management remains to be established.

12. Novel therapies

- a. **ω-3 polyunsaturated fatty acids (PUFA)** have demonstrated an ability to reduce heart failure–associated morbidity and mortality and are now considered a reasonable intervention in patients with NYHA functional class II–IV symptoms by the Heart Failure Society of America. The **Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto Miocardico Heart Failure (GISSI-HF)** trial demonstrated that 1 g/d of PUFAs resulted in a reduction in all-cause mortality. Recent data suggest that higher doses of PUFAs used in patients with milder heart failure symptoms due to nonischemic cardiomyopathy may result in a dramatic reduction in heart failure hospitalizations. The formulation of PUFA used is important, as there does appear to be a dose–response effect. Formulations containing at least 1 g of eicosapentaenoic acid and docosahexaenoic acid appear to be required for benefit.

C. Chronic nonmedical therapies

1. **Patient education and disease management programs** remain the most effective treatment strategy for patients with systolic heart failure. Sodium restriction (<2,000 mg daily) and medication compliance are crucial to reducing hospitalizations. Control of blood pressure, serum glucose, and lipid levels should be emphasized. Some highly motivated patients can perform self-monitoring (i.e., daily weights and symptom assessment) and care (i.e., titration of diuretics) analogous to the chronic management of diabetes.
2. **Exercise training.** There is a clear body of evidence supporting the fact that exercise training improves endothelial function and functional capacity in patients with chronic heart failure. A supervised cardiac rehabilitation program should be advised when available.

- D. **Advanced therapies.** Mechanical circulatory support and orthotopic heart transplantation are therapies currently reserved for patients with ACC/AHA stage D heart failure refractory to other therapies. These are described in detail in Chapters 12 and 13, respectively.

VIII. PROGNOSIS. Heart failure is associated with high rates of morbidity and mortality. In the Framingham Heart study, patients with heart failure had mortality rates four to eight times those of age-matched controls. A patient with NYHA class IV heart failure has a 1-year survival between 30% and 50%—a mortality rate comparable to that of advanced malignancies. Several risk scores have been developed to characterize the risk of heart failure hospitalization and mortality. The Seattle Heart Failure Model is perhaps the most widely used of these and incorporates demographic, clinical, pharmacologic, and laboratory data to provide accurate 1-, 2-, and 3-year survival estimates. Table 8.5 lists some common clinical predictors of poor survival in systolic heart failure.

TABLE 8.5 Common Clinical Predictors of Poor Prognosis in Systolic Heart Failure

- Increased age
- Male gender
- Increased New York Heart Association functional class
- Severely reduced LV ejection fraction (< 25%), extensive cardiac remodeling (LVIDd > 65 mm), or reduced cardiac index (< 2.5)
- Concomitant diastolic dysfunction (particularly irreversible restrictive filling, stage IV diastolic dysfunction)
- Reduced right ventricular function

(Continued)

TABLE 8.5 Common Clinical Predictors of Poor Prognosis in Systolic Heart Failure (*Continued*)

- Atrial fibrillation, elevated average heart rate, and reduced heart rate variability
- Low peak Vo_2 with maximal exercise (14 mL/min/kg), low heart rate response to exercise, increased peripheral chemosensitivity (ventilatory response to hypoxia), and high V_E/VCO_2
- High plasma BNP and N-terminal proBNP levels
- High levels of other cardiac and neurohormonal biomarkers including norepinephrine, renin, arginine vasopressin, aldosterone, endothelin-1, tumor necrosis factor, cardiac troponin T and I, and C-reactive protein
- Anemia
- Markers of reduced tissue perfusion:
 - Low mean arterial pressure
 - Renal insufficiency (creatinine clearance < 60 mL/min)
 - Attenuated response to diuretics and lack of hemodynamic and structural improvement (reverse remodeling) with medical therapy
 - Persistent signs of congestion and fluid retention or failure to normalize filling pressures (PCWP < 16 mm Hg, CVP < 8 mm Hg) with medical therapy
 - Serum sodium < 135 mg/dL
- Cardiac dyssynchrony (QRS > 130 milliseconds, left bundle branch block)
- Depression
- Nocturnal Cheyne-Stokes respiration and obstructive sleep apnea

BNP, B-type natriuretic peptide; CVP, central venous pressure; LV, left ventricular; LVIDd, left ventricular internal dimension at diastole; PCWP, pulmonary capillary wedge pressure.

ACKNOWLEDGMENTS: *The authors would like to thank Dr. Brian Hardaway for his contributions to earlier editions of this chapter.*

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USEFUL WEB SITES

- Seattle Heart Failure Model: <http://depts.washington.edu/shfm/>
- HFSA Heart Failure Guidelines: <http://www.heartfailureguidelines.org/>

Heart Failure with Preserved Ejection Fraction and Restrictive Cardiomyopathy

I. INTRODUCTION

- A. Epidemiologic studies suggest that nearly one-half of patients with heart failure have a normal ejection fraction; the proportion in those hospitalized has been reported to range from 24% to 55%. The survival of patients with heart failure and preserved ejection fraction was once thought to be better than those with a decreased ejection fraction, but recent evidence suggests similar mortality rates.

Heart failure with preserved ejection fraction (HFpEF) has become the preferred term in the literature. This clinical entity has also been referred to as diastolic heart failure and heart failure with preserved ejection fraction. In this chapter, we focus on HFpEF and provide a brief discussion of the restrictive cardiomyopathies, which are important differential diagnoses in patients presenting with heart failure and a normal ejection fraction.

- B. **Definition.** In the latest consensus document (by the European Working Group), HFpEF is defined as (1) **signs and symptoms of congestive heart failure**; (2) **left ventricular ejection fraction (LVEF) > 50% and a nondilated left ventricle (<97 mL/m²)**; (3) **evidence of elevated left ventricular (LV) filling pressures (Table 9.1)**. The last criterion is fulfilled in one of three ways: (1) invasive hemodynamics (pulmonary capillary wedge pressure [PCWP] > 12 mm Hg or left ventricular end-diastolic pressure [LVEDP] > 16 mm Hg), (2) unequivocal echocardiographic evidence of elevated LV filling pressure ($E/e' > 15$), or (3) equivocal echocardiographic evidence ($E/e' > 8$ but < 15) **and** a positive β -natriuretic peptide (BNP) (NT-BNP > 220 pg/mL or BNP > 200 pg/mL).
- C. **Pathophysiology.** Most pathophysiologic abnormalities in patients with HFpEF are related to diastolic function. There are two major determinants of diastolic function: LV relaxation and LV stiffness. LV relaxation relates to the cellular mechanisms involved with actin–myosin crossbridge detachment. This requires intracellular calcium uptake into the sarcoplasmic reticulum, an energy- or adenosine triphosphate (ATP)-dependent process. Thus, ischemia, which would decrease intracellular availability of ATP, would prolong the time required for ventricular relaxation. LV stiffness relates to the compliance of the myocardial tissue. One determinant of this is the extracellular matrix. For example, increase in fibrosis and collagen deposition, as in patients with hypertensive heart disease, leads to an increase in LV stiffness. Restrictive cardiomyopathies share a similar pathophysiology, with increased LV stiffness; however, these differ in the pathology underlying the change in ventricular compliance: extracellular amyloid deposition (cardiac amyloidosis); endocardial fibrosis from eosinophilic injury (Löffler's endocarditis and endomyocardial fibrosis); intracellular lysosomal engorgement with sphingolipids (Fabry's disease); and others.

TABLE 9.1 Diagnostic Criteria for Heart Failure with Preserved Ejection Fraction

Clinical	Signs and symptoms of CHF
Left ventricular size and function	Non dilated ($< 97 \text{ mL/m}^2$), EF $> 50\%$
Hemodynamics (one of the following conditions must be met)	<ol style="list-style-type: none"> 1. LVEDP $> 16 \text{ mm Hg}$ or PCWP $> 12 \text{ mm Hg}$ 2. $E/e' > 15$ 3. If $E/e' > 8$ but < 15, then BNP must be elevated (NT-BNP $> 220 \text{ pg/mL}$ or BNP $> 200 \text{ pg/mL}$)

CHF, congestive heart failure; EF, ejection fraction; LVEDP, left ventricular end-diastolic pressure; PCWP, pulmonary capillary wedge pressure; BNP, β -natriuretic peptide.

A number of other pathophysiologic mechanisms have been implicated in patients with HFpEF. These include arterial stiffness, the relationship between arterial and ventricular stiffness, and chronotropic incompetence. The implications and relative importance of these mechanisms are still unclear.

II. CLINICAL PRESENTATION

- A. **Demographics.** When compared with patients with systolic dysfunction, those with HFpEF tend to be older and are more likely to be female. Associated comorbidities include hypertension, diabetes, obesity, and chronic kidney disease.
- B. **Symptoms.** Analogous to systolic dysfunction, diastolic dysfunction spans the spectrum of asymptomatic or subclinical disease to those with an established clinical syndrome of congestive heart failure. The symptoms of diastolic heart failure are indistinguishable from those of systolic heart failure. It may present with only exertional fatigue or dyspnea symptoms. Other patients will have more overt symptoms of left-sided (dyspnea, orthopnea, and paroxysmal nocturnal dyspnea) and right-sided (edema and abdominal bloating) heart failure.
- C. **Signs.** The signs of HFpEF are similar to those for systolic heart failure. One should look for the typical signs of right-sided (elevated jugular venous pressure, hepatic congestion, ascites, and lower extremity edema) and left-sided (rales) congestion. The presence of an S4 usually signifies a stiff left ventricle. As opposed to those patients with dilated cardiomyopathies, the location of the apical impulse is usually close to the midclavicular line, signifying a normal-sized ventricle. One should also pay attention to the strength of the impulse; in patients who do not have thick chest walls, a hypertrophied ventricle will often have a stronger impulse than the one without left ventricular hypertrophy (LVH). In patients with exertional symptoms alone, the above signs may not be present as the manifestation of their diastolic dysfunction may occur only during exercise.

In patients who present with impressive right-sided heart failure features, particularly ascites and hepatic congestion, restrictive cardiomyopathy or constrictive pericarditis or a combination should be considered. In these patients, clinical findings of multiorgan disease may indicate specific etiologies of restrictive cardiomyopathy. The cardiac examination may demonstrate more specific findings, including Kussmaul's sign: a paradoxical elevation in the mean jugular venous pressure during inspiration. This is classically described in constrictive pericarditis but can be seen in patients with restrictive cardiomyopathy as well as other pathologies (severe right ventricular failure and tricuspid regurgitation).

III. LABORATORY EXAMINATION AND BASIC INVESTIGATIONS

- A. **Electrocardiogram (ECG).** ECG is an insensitive test for HFpEF. In this scenario, the most important finding is the amplitude of QRS voltage. The presence of elevated voltages and other criteria for LVH would support this as a possible cause of HFpEF. Conversely, in a patient who has increased wall thickness (typically by echocardiography) but has low voltage or infarction patterns on ECG (in this case, “pseudoinfarction”), infiltrative or restrictive cardiomyopathy should be considered.
- B. **Chest radiograph.** The chest x-ray has few specific findings for HFpEF. In a posterior–anterior film, a normal-sized heart (lateral heart width $< 2/3$ of a hemithorax) may be a clue to a normal-sized left ventricle. Otherwise, the findings are the same as in systolic dysfunction: fluffy alveolar opacities (alveolar pulmonary edema), increased interstitial markings (increased interstitial fluid), pulmonary vascular redistribution (increased pulmonary venous pressures), and pleural effusions.
- C. **Specific laboratory investigations.** BNP can be helpful in establishing the diagnosis of HFpEF (as stated above). When compared with patients with systolic heart failure, the elevation in BNP is generally lower. In patients with undifferentiated dyspnea, a normal BNP would argue against the presence of any heart failure syndrome.

IV. DIFFERENTIAL DIAGNOSIS. For the purposes of our discussion, there are two clinical presentations to consider: exertional dyspnea (without findings of heart failure) and congestive heart failure.

In a patient presenting primarily with exercise intolerance or exertional dyspnea, HFpEF should be considered, in addition to silent coronary artery disease, primary lung disease, anemia, etc.

In a patient who has an established clinical syndrome of heart failure, the differential diagnosis is typically narrowed following echocardiography. In a patient with preserved ejection fraction and a normal-sized left ventricle, HFpEF is the most likely cause. Other entities to consider include restrictive cardiomyopathies, hypertrophic cardiomyopathy (HCM), valvular heart disease, and constrictive pericarditis. Here, we primarily discuss HFpEF and restrictive cardiomyopathies.

- A. **HFpEF.** Heart failure without another obvious cause, particularly in the context of advanced age, hypertension, obesity, chronic kidney disease, and diabetes, should lead to an early consideration for HFpEF. In such patients, myocardial ischemia may play some role in the manifestation of heart failure. This is particularly true for patients presenting with acute heart failure or flash pulmonary edema. In the absence of dynamic valvular regurgitation, ischemia leading to pulmonary edema usually denotes a large amount of myocardium at risk. This type of presentation certainly warrants aggressive investigation for obstructive coronary disease and when applicable, revascularization. Whether or not ischemia plays a role in patients with more subacute or chronic heart failure presentations is debatable.
- B. **Hypertrophic cardiomyopathy.** The diagnosis of HCM is usually made in the presence of LVH, without concomitant hypertension or aortic stenosis. There are many manifestations of HCM, one of which is a “restrictive” phenotype that presents predominantly with diastolic heart failure. Distinction between HCM and other restrictive cardiomyopathies is not always clear, but it should be considered in certain scenarios: examples of this would include family members with HCM (particularly with an identified gene mutation), the typical reverse curve morphology of the interventricular septum, predilection for sudden death or ventricular tachyarrhythmia, and/or the presence of LV outflow tract obstruction.
- C. **Restrictive cardiomyopathies.** Restrictive cardiomyopathies represent a group of disorders in which ventricular stiffness is increased by mechanisms/pathologies other than those related to the more garden-variety HFpEF patients. This may be a result of infiltrative, inflammatory, or metabolic diseases. The most common etiology of restrictive cardiomyopathy is cardiac amyloidosis.

1. **Cardiac amyloidosis.** Amyloidosis refers to the deposition of amyloid, or an abnormal protein, in organ tissue. There are several causes, and the following are the most important ones that manifest with cardiac involvement.
 - a. Primary amyloidosis is caused by a primary hematologic malignancy. Monoclonal plasma cells produce a light-chain immunoglobulin; deposition into cardiac tissue is variable. Early stages show subclinical diastolic dysfunction (usually seen on echocardiography); later stages show severe restrictive cardiomyopathy. Traditionally, patients presenting with heart failure are felt to have a very poor prognosis with limited treatment options. However, anecdotal experience suggests that achieving remission of the malignancy with chemotherapeutics may positively impact patient's heart failure symptoms.
 - b. Familial amyloidosis involves the inheritance of a gene that produces a mutant form of transthyretin, a serum protein carrier of thyroxine and retinol. The protein is produced in the liver and is deposited in the kidneys, the heart, and the nerves. Some centers may offer cardiac transplantation to selected patients.
 - c. Senile amyloidosis is similar to familial amyloidosis in that it is related to the deposition of a pathologic variant of transthyretin. This usually occurs in older men.
2. **Endomyocardial fibrosis.** Endomyocardial fibrosis occurs in areas close to the equator, such as equatorial Africa, South America, and Asia. It usually affects children and young adults. Histologically it is characterized by granulation tissue, collagen, and extensive connective tissue lining the endocardium. It affects both ventricles (50%), left ventricle (40%), or isolated right (10%) ventricle and is associated with a 2-year mortality rate of up to 50%. Atrial fibrillation, mitral regurgitation, and thromboembolism are common. The response to medical treatment is poor. Endocardial decortication may be beneficial for those with New York Heart Association (NYHA) class III or IV symptoms. This technique has high operative mortality (15% to 20%), but when successful, reduces symptoms and may favorably affect the survival.
3. **Loeffler's (eosinophilic) endocarditis.** Loeffler's endocarditis is more commonly seen in temperate climates and generally occurs as part of the idiopathic hypereosinophilic syndrome. It typically manifests in middle age. Features include eosinophilia, restrictive cardiomyopathy, and nervous system and marrow involvement. Left ventricular mural thrombus frequently occurs. Aside from conventional heart failure medications (including anticoagulation), corticosteroids and hydroxyurea are useful treatment options. Surgery may be required for advanced fibrotic disease.
4. **Idiopathic restrictive cardiomyopathy.** Idiopathic restrictive cardiomyopathy is a diagnosis of exclusion. It usually occurs sporadically, but may be inherited with an autosomal dominant pattern in association with distal skeletal myopathy and occasionally a heart block. Echocardiography reveals near-normal LV dimensions and function, biatrial enlargement, and variable hypertrophy. Endomyocardial biopsy is unremarkable or shows nonspecific changes. The condition may manifest at any age throughout childhood or adult life. Survival time varies, with a mean survival of 9 years. Cardiac transplantation may be indicated in selected patients.
5. **Sarcoidosis.** Cardiac sarcoidosis can present with restrictive cardiomyopathy, but much more commonly it produces a dilated cardiomyopathy phenotype. Associated cardiac manifestations include conduction disease and ventricular tachyarrhythmia.
6. **Radiation carditis.** Radiation heart disease affects almost all components of the heart. Direct myocardial involvement, usually in the form of diastolic dysfunction, can be underappreciated, particularly when there is concomitant valvular, coronary, and/or pericardial disease. Separating the relative contributions of multiple pathophysiologic mechanisms in a given radiation patient is extraordinarily challenging. This is particularly evident when these patients go to surgery for

correction of valvular, coronary, and/or pericardial disease; suboptimal outcomes despite these corrections may be related to residual myocardial disease.

7. **Metabolic storage diseases** are characterized by intracellular deposition of substances within the myocyte, resulting in increased myocardial stiffness.
 - a. **Hemochromatosis**, or iron overload, is listed as a storage disorder that can cause restrictive cardiomyopathy. However, when cardiac manifestations occur, the phenotype is usually a dilated cardiomyopathy.
 - b. **Glycogen storage diseases**. Types II, III, IV, and V glycogen storage diseases may present with cardiac manifestations, usually as asymptomatic increase in LV thickness.
 - c. **Gaucher's disease**. Gaucher's disease is caused by a deficiency in β -glucosidase, which leads to cerebroside deposition into multiple organs (spleen, liver, brain, bone marrow, lymph nodes, and heart). In the heart, this can cause increased ventricular thickness with diastolic dysfunction, LV systolic dysfunction, pericardial effusion, and valvular disease. This can be treated with enzyme replacement.
 - d. **Fabry's disease** is a lysosomal storage disease caused by a deficiency in α -galactosidase (X-linked, recessive trait). This leads to glycosphingolipid accumulation in the kidney, the skin, and the heart. Cardiac manifestations include increased LV thickness, diastolic dysfunction, AV block, and mitral regurgitation. This can be treated with enzyme replacement.

V. DIAGNOSTIC TESTING

- A. **Echocardiography** is the primary modality in evaluating a patient with a clinical syndrome of congestive heart failure. It is the modality of choice when evaluating LV diastolic function (Fig. 9.1). The most commonly used parameter in clinical practice is the Doppler interrogation of the transmitral flow pattern and tissue Doppler evaluation of annular velocity to determine the E/e' ratio. There are numerous other 2D and Doppler findings that are critical to diagnosis, including chamber size and wall thickness.

1. **Transmitral flow pattern**. In sinus rhythm, using pulsed wave Doppler across the mitral inflow tract generates two waves: the early E wave, corresponding to rapid ventricular filling as the mitral valve opens, and the A wave, which reflects atrial contraction. In healthy people younger than 50 years, E is larger than A (i.e., E/A ratio > 1). The E-wave deceleration time is the time from peak E inflow

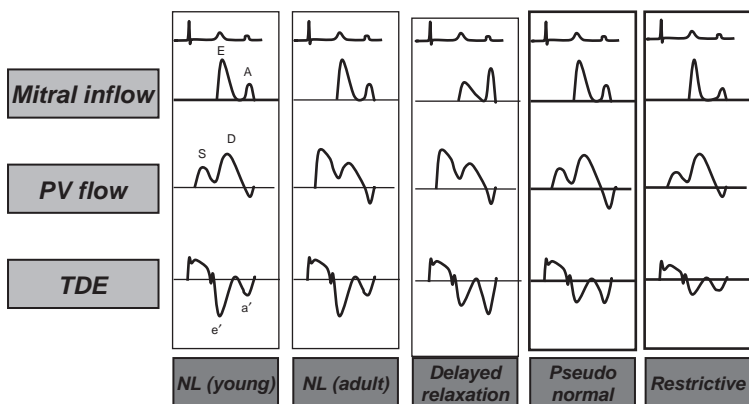


FIGURE 9.1 Patterns of diastolic function. PV flow, pulmonary vein flow; TDE, tissue Doppler (mitral annulus); NL, normal.

velocity to decay to zero. With age, hypertension, or ischemia, the viscoelastic properties of the ventricle decrease, and the E wave decreases in amplitude, has a gentler slope, and has a longer deceleration time. The atrial kick is proportionately greater, and E–A reversal occurs, with an E/A ratio < 1 (grade 1 diastolic dysfunction). With progression of diastolic dysfunction, left atrial (LA) pressure rises further to compensate, and the E wave becomes more prominent than the A wave (i.e., pseudonormalization or grade 2 diastolic dysfunction). As diastolic dysfunction progresses, the LV stiffness increases and the deceleration time shortens, reflecting rapid equilibration of LA/LV pressures during early diastole. When the deceleration time is < 160 milliseconds and the E/A ratio is > 2 , the patient is considered to have grade 3 diastolic dysfunction.

Although the transmitral flow pattern is one of the primary ways of evaluating diastolic function, it has several limitations. It can be difficult to differentiate normal diastolic function from the “pseudonormal” pattern of grade 2 diastolic dysfunction, as they both have E/A ratios > 1 . Because of this, American Society of Echocardiography guidelines have assigned stronger weight to other findings, including tissue Doppler imaging (TDI) and LA chamber size. Also, the transmitral flow pattern can often be difficult to interpret or uninterpretable in common scenarios, including atrial fibrillation, tachycardia (fusion of E and A waves), and mitral valve disease (MR $\geq 3+$, mitral stenosis, and mitral prosthesis).

2. **Tissue Doppler imaging (TDI) of the mitral annular velocity.** In the evaluation of LV diastolic function, TDI is used to measure the velocity of movement of the septal and lateral aspects of the mitral annulus. The myocardial velocities have three main components: systolic wave (S'), early diastolic wave (e'), and the late diastolic wave (a'). In the earliest stages of diastolic dysfunction, the diastolic velocities of annular motion decrease. Normally, the lateral annulus tends to have higher velocities than the septal mitral annulus. Septal $e' < 8$ cm/s and/or a lateral $e' < 10$ cm/s suggests the presence of diastolic dysfunction.

Unlike the transmitral flow pattern, there is no “pseudonormalization” pattern with annular velocity, making it easier to differentiate normal from abnormal diastolic function. The mitral annular TDI should be used with caution when other conditions coexist that may affect annular velocity independent of ventricular relaxation such as infarction of the septum or lateral wall or constriction with pericardial adhesion of the lateral wall.

3. **E/e'.** The ratio of the E velocity (obtained from the transmitral flow pattern) and the e' (obtained from TDI primarily of the lateral mitral annulus) can be used to estimate filling pressure, as there is a rough correlation with invasive hemodynamics (PCWP). This correlation is better with patients with depressed ejection fraction but is reasonable in patients with normal ejection fraction. Extreme values are most helpful. $E/e' < 8$ correlates with normal LV filling pressures. $E/e' > 15$ correlates with PCWP > 12 mm Hg; higher values are more specific for this. Unfortunately, there are many patients that fall into the intermediate zone, where $E/e' > 8$ but < 15 . For these patients, the presence of elevated filling pressure cannot be determined by this method alone. Echocardiographic guidelines suggest using the presence of LA enlargement (LA volume index > 34 mL/m²). Plasma BNP may be helpful in equivocal cases to determine whether or not there is corroborating evidence for elevated pressures.

In patients with predominantly **exertional** symptoms, it may be useful to perform exercise echocardiography to determine the presence of diastolic dysfunction during exertion, particularly when this is not evident at rest. The sonographer should obtain LV images in multiple views following stress. Once the 2D information has been acquired, Doppler studies, including the transmitral flow pattern and the TDI of the septal and lateral mitral annulus, should be recorded. The diastolic abnormalities usually persist after tachycardia subsides, so

it is recommended that the data are recorded for a period of time following stress to reduce the likelihood of E- and A-wave fusion, which would make the E-wave velocity difficult to interpret. The most important parameter is E/e' following stress; if it is > 15, exertional increase in LV filling pressures is likely.

- B. Invasive hemodynamic assessment.** Invasive hemodynamic assessment is not routinely performed but is indicated when it is unclear whether elevated filling pressures are present on noninvasive studies. The PCWP (> 12 mm Hg) or LVEDP (> 16 mm Hg) should be measured. Other diastolic parameters, including Tau (τ), the time constant of isovolumic relaxation, are rarely measured in clinical practice.

When restrictive cardiomyopathy is considered, detailed hemodynamics may be of greatest value in directing management but are often less helpful in differentiating between possible diagnoses. Findings such as elevated and equalized diastolic pressures in four chambers (within 5 mm Hg), M pattern of the right atrial pressure waveform, "dip and plateau" of the ventricular diastolic pressures, equalization of LVEDP/RVEDP, and Kussmaul's sign occur in a number of pathologies, including restrictive cardiomyopathy, constrictive pericarditis, severe right ventricular failure, and severe tricuspid regurgitation.

- C. Magnetic resonance imaging (MRI).** In most patients with a diagnosis of HFpEF, cardiac MRI is rarely needed. It is useful to measure ventricular function, mass, and volumes when echocardiography is not diagnostic. It is also helpful in establishing or excluding specific conditions such as constrictive pericarditis, sarcoidosis, amyloidosis, or hemochromatosis (see Chapter 51).
- D. Endomyocardial biopsy.** Endomyocardial biopsy is used in selected circumstances, particularly when there is a high suspicion of a disorder whose diagnosis will profoundly impact management and prognosis. The most common indication is when cardiac amyloidosis is suspected. Biopsy in this setting can determine the presence of amyloid as well as differentiate between the different types of amyloid. The yield of endomyocardial biopsy for patchy diseases, such as sarcoidosis, is low.

VI. THERAPY. A handful of trials have attempted to look at the role of a variety of agents, including angiotensin receptor blockers (ARBs), angiotensin-converting enzyme (ACE) inhibitors, and β -blockers in patients with HFpEF. Unfortunately, **none of these trials have shown mortality benefit**. There has been variable effect of these medications on morbidity end points, including heart failure hospitalizations, symptoms, and LVH regression. The relevance of some of these trials is in question, as their entry criteria included patients with LV dilation and LVEF < 50%, likely a population quite different from our current conception of HFpEF patients. As the literature currently stands, no specific treatment has clearly demonstrated mortality benefit in patients with HFpEF. Treatment of hypertension should be in accordance with JNC VII guidelines (the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure). Otherwise, treatment should be aimed toward symptomatic relief. The current ACC/AHA 2009 guidelines are listed in Table 9.2.

- A. Salt restriction.** Patients should be placed on a salt-restricted diet, usually 2,000 mg of sodium daily.
- B. Diuretics.** Diuretics should be used for symptomatic treatment of edema and pulmonary congestion. Chronic use of loop diuretics may lead to diuretic resistance; in this scenario, a thiazide- or potassium-sparing diuretic may be used to augment diuresis. For this indication, hydrochlorothiazide (usually 50 mg dosage, given once or intermittently) is effective within the first day. In extreme cases, patients may have significant bowel edema, rendering diuretics with poor oral absorption ineffective. In these patients, torsemide, which has a better oral absorption profile, is a reasonable option. Diuresis is often limited by the occurrence of prerenal azotemia. This is particularly common in those HFpEF or restrictive cardiomyopathy patients with

TABLE 9.2 Guidelines Adapted from ACC/AHA 2009 Update**Class I guidelines**

Control systolic and diastolic hypertension	Physicians should control hypertension in accordance with published guidelines (level of evidence: A)
Diuretics	Physicians should use diuretics to control pulmonary congestion and peripheral edema (level of evidence: C)
Ventricular rate should be controlled in the presence of AF	Physicians should control ventricular rate in AF (level of evidence: C)

Class IIa guidelines

Coronary revascularization	In patients with CAD in whom ischemia is having an adverse effect on cardiac function (level of evidence: C)
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Class IIb guidelines

Restoration and maintenance of sinus rhythm	May be useful in improving symptoms (level of evidence: C)
Digoxin	Usefulness in reducing symptoms is not well established (level of evidence: C)
β -Blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, or calcium antagonists and controlled hypertension	Might be effective in minimizing symptoms (level of evidence: C)

AF, atrial fibrillation; CAD, coronary artery disease.

systemic disorders that have concomitant effects on the kidney, including hypertension, diabetes, or amyloidosis. In these cases, balancing congestive symptoms and azotemia can be challenging. On occasion, the patient may only achieve symptomatic relief after aggressive diuresis, even to the point where the blood urea nitrogen and/or creatinine are at levels higher than baseline values.

- C. Angiotensin receptor blockers.** Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity Programme (CHARM-P) and Irbesartan in Heart Failure with Preserved Ejection Fraction Study (I-PRESERVE) are two trials that evaluated the use of ARBs in the HFpEF population. I-PRESERVE is arguably the most relevant trial, as it enrolled patients with LVEF $\geq 45\%$ and randomized patients to irbesartan versus placebo. This trial showed no difference in the primary end point of mortality and heart failure hospitalizations between the active and placebo groups. CHARM-P, which randomized candesartan versus placebo also failed to show a difference in a similar primary end point; the secondary end point of heart failure hospitalizations did seem to be reduced in the candesartan arm.
- D. ACE inhibitors.** The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) trial randomized patients with LVEF $> 40\%$ to perindopril versus placebo. The primary end point was not met, but after 1 year, there appeared to be a statistically significant decrease in heart failure hospitalizations in the active treatment arm.
- E. Beta-blockers.** The Study of the Effects of Nebivolol Intervention on Outcomes and Rehospitalisation in Seniors with Heart Failure (SENIORS) trial randomized

nebivolol versus placebo in all-comers with congestive heart failure. Thirty-five percent of the patients had LVEF > 35%. In the overall trial, the nebivolol group demonstrated a significant decrease in the primary end point of mortality and heart failure mortality. In the subgroup analysis, the improvement appeared to hold in the group with LVEF > 35%.

- F. **Digoxin.** The Digitalis Investigation Group (DIG) trial evaluated the use of digoxin in patients with heart failure. A subgroup of that trial examined patients with LVEF > 45%. There was no significant difference in mortality in this subgroup. There was a nonsignificant trend toward decreased heart failure hospitalizations but an increased trend toward unstable angina hospitalizations in those treated with digoxin.
- G. **Spironolactone.** In patients with depressed ejection fraction, aldosterone antagonists have been demonstrated to have beneficial effects, likely working through antifibrotic mechanisms. There are two ongoing pivotal trials, Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist (TOPCAT) and Aldosterone Receptor Blockade in Diastolic Heart Failure (ALDO-HF), designed to evaluate the use of spironolactone in patients with HFpEF.
- H. **Sildenafil.** Currently, there is no indication for phosphodiesterase 5 inhibitors in HFpEF, and mechanistic studies are ongoing.

VII. PRACTICAL APPROACH TO HFpEF AND RESTRICTIVE CARDIOMYOPATHIES

- A. **Exertional dyspnea only.** In these patients, HFpEF should be on the differential diagnosis. Resting echocardiogram should be performed, with particular attention paid toward the presence of resting diastolic dysfunction. If this is absent, one can consider exercise echocardiography to determine exercise-induced diastolic dysfunction. Even in the presence of this diagnosis, specific treatment or change in management is uncertain.
- B. **Congestive heart failure.** For patients presenting with overt signs of congestive heart failure, echocardiography should be used to narrow the differential diagnosis. In the absence of findings to support LV systolic dysfunction, valvular disease, or constrictive pericarditis, one should consider HFpEF as the diagnosis if there is evidence of diastolic dysfunction and elevated LV filling pressures. This is determined by unequivocal echocardiographic evidence ($E/e' > 15$); equivocal echocardiographic evidence ($E/e' > 8$ and < 15) + elevated BNP (NT-BNP > 200 pg/mL or BNP > 200 pg/mL); or invasive hemodynamics (PCWP > 12 mm Hg, LVEDP > 16 mm Hg). If the above findings are met and the patient fits the appropriate demographic (elderly, female, hypertension, chronic kidney disease, diabetes, and obese), then HFpEF is a reasonable diagnosis.

Restrictive cardiomyopathy should be entertained when patients present with significant right-sided heart failure symptoms (ascites, hepatic congestion, and severe edema), have multiorgan presentations (amyloidosis—orthostasis and renal failure; Fabry's—renal and skin involvement), or do not fit the typical demographic for HFpEF (young and no hypertension). In these patients, additional, focused testing should be performed to establish the etiologic diagnosis. This may include cardiac MRI and, in selected circumstances, endomyocardial biopsy.

- C. **Treatment.** To date, there has been no class of medications that has been clearly established to have mortality benefit for patients with HFpEF. As it is believed that hypertension is the underlying etiology in most patients with HFpEF, blood pressure in these should be treated according to the established guidelines. However, particular agents do not have a priority as they do in patients with depressed ejection fraction, because they have not yet been demonstrated to have the same mortality and morbidity benefits. Otherwise, diuretics should be used for symptomatic benefit. The importance of concomitant obstructive coronary artery disease is debatable in asymptomatic patients. Likewise, revascularization should be reserved for patients in which ischemia is thought to play a major, adverse role in cardiac function (Table 9.2).

For those patients with restrictive cardiomyopathy, treatment should be directed toward the specific etiology. Oftentimes, there are no therapies that can reverse the severity of the restrictive cardiomyopathy, and the presence of congestive heart failure portends a poor prognosis. In these patients, diuretics are used for symptomatic relief. In selected candidates, cardiac transplantation may be entertained.

VIII. PROGNOSIS. HFpEF was once thought to confer a better prognosis than systolic dysfunction. Recent evidence demonstrates that the survival rates in both cases are similar. Twenty-two percent to 29% of patients with HFpEF die within 1 year of being discharged from their first hospitalization; 65% die within 5 years. Unlike patients with systolic dysfunction, no effective treatment has been found to improve this dismal outcome. The two groups have also been found to have similar rates of readmission for heart failure.

ACKNOWLEDGMENTS: *The authors thank Drs. Ryan P. Daly, John G. Peterson, and W.H. Wilson Tang for their contributions to earlier editions of this chapter. Special thanks to Dr. Allan Klein for his contributions to the figures of this chapter.*

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Hypertrophic Cardiomyopathy

- I. INTRODUCTION.** The generally accepted definition of hypertrophic cardiomyopathy (HCM) is left ventricular (LV) hypertrophy associated with nondilated ventricular chambers in the absence of another cardiac or systemic disease that itself could produce such hypertrophy. There are many causes of LV wall thickening (Table 10.1), including long-standing hypertension, aortic stenosis, and infiltrative cardiomyopathies. However, these diseases can typically be identified by noninvasive markers, such as a history of significant hypertension and severe aortic stenosis. Other diseases will be identified by multisystem organ involvement (e.g., skeletal muscle weakness in Danon disease). HCM can be identified by a constellation of abnormalities, including gene mutations, marked LV thickness (> 25 mm), the presence of left ventricular outflow tract (LVOT) obstruction, and/or the presence of systolic anterior motion (SAM).

While there are many alternative names for HCM, including *idiopathic hypertrophic subaortic stenosis*, *hypertrophic obstructive cardiomyopathy*, and *muscular subaortic stenosis*, the World Health Organization (WHO) recommends that HCM should be used. It is the preferred term because it does not imply that obstruction (present in only approximately 25% of cases) is an invariable component of the disease.

II. CLINICAL PRESENTATION

A. Natural history

1. The **histological features** of HCM are disarray of cell-to-cell arrangement, disorganization of cellular architecture, and fibrosis. The most common sites of ventricular involvement are, in decreasing order, the septum, apex, and mid-ventricle. One-third of patients have wall thickening limited to one segment. These morphologic and histological features, which vary in phenotypic and clinical expression, give rise to the characteristically unpredictable natural history of HCM.
2. The **prevalence** of HCM is approximately 1 in 500, and the condition appears to be familial in origin. This makes HCM one of the most common genetically transmitted cardiovascular diseases. It is found among 0.5% of unselected patients referred for echocardiographic examination and is a leading cause of sudden death among athletes younger than 35 years.

B. Signs and symptoms

1. **Heart failure.** Symptoms, which include dyspnea, dyspnea on exertion, paroxysmal nocturnal dyspnea, and fatigue, are largely a consequence of two processes: elevated LV diastolic pressure caused by diastolic dysfunction and dynamic LV outflow obstruction.
 - a. Events that accelerate heart rate, decrease preload, shorten diastolic filling time, increase LV outflow obstruction (i.e., exercise and tachyarrhythmias), or worsen compliance (i.e., ischemia) exacerbate these symptoms.

TABLE 10.1 Differential Diagnosis of Left Ventricular Wall Thickening	
1	Myocardial infarction
2	Myocarditis
3	Cardiomyopathy (hypertrophic, dilated, restrictive)
4	Coronary artery disease
5	Valvular disease
6	Pericardial disease
7	Conduction system disease
8	Structural heart disease
9	Genetic disorders
10	Systemic diseases
11	Drug-induced
12	Postoperative
13	Posttraumatic
14	Postinfectious
15	Postneoplastic
16	Postischemic
17	Posthypertensive
18	Postcardiomyopathic
19	Postvalvular
20	Postpericardial
21	Postconduction system
22	Poststructural heart
23	Postgenetic
24	Postsystemic
25	Postdrug-induced
26	Postoperative
27	Posttraumatic
28	Postinfectious
29	Postneoplastic
30	Postischemic
31	Posthypertensive
32	Postcardiomyopathic
33	Postvalvular
34	Postpericardial
35	Postconduction system
36	Poststructural heart
37	Postgenetic
38	Postsystemic
39	Postdrug-induced
40	Postoperative
41	Posttraumatic
42	Postinfectious
43	Postneoplastic
44	Postischemic
45	Posthypertensive
46	Postcardiomyopathic
47	Postvalvular
48	Postpericardial
49	Postconduction system
50	Poststructural heart
51	Postgenetic
52	Postsystemic
53	Postdrug-induced
54	Postoperative
55	Posttraumatic
56	Postinfectious
57	Postneoplastic
58	Postischemic
59	Posthypertensive
60	Postcardiomyopathic
61	Postvalvular
62	Postpericardial
63	Postconduction system
64	Poststructural heart
65	Postgenetic
66	Postsystemic
67	Postdrug-induced
68	Postoperative
69	Posttraumatic
70	Postinfectious
71	Postneoplastic
72	Postischemic
73	Posthypertensive
74	Postcardiomyopathic
75	Postvalvular
76	Postpericardial
77	Postconduction system
78	Poststructural heart
79	Postgenetic
80	Postsystemic
81	Postdrug-induced
82	Postoperative
83	Posttraumatic
84	Postinfectious
85	Postneoplastic
86	Postischemic
87	Posthypertensive
88	Postcardiomyopathic
89	Postvalvular
90	Postpericardial
91	Postconduction system
92	Poststructural heart
93	Postgenetic
94	Postsystemic
95	Postdrug-induced
96	Postoperative
97	Posttraumatic
98	Postinfectious
99	Postneoplastic
100	Postischemic

- Long-standing hypertension
- Athlete's heart
- Aortic stenosis
- Amyloidosis
- Mitochondrial disease
- Fabry disease
- Friedreich's ataxia
- Danon disease
- Noonan syndrome
- Pompe disease

- b. Between 5% and 10% of patients with HCM progress to severe LV systolic dysfunction, characterized by progressive LV wall thinning and cavity enlargement.
- 2. **Myocardial ischemia.** Myocardial ischemia occurs in obstructive and nonobstructive HCM.
 - a. The **clinical and electrocardiographic** presentation is similar to that of ischemic syndromes in persons without HCM. Ischemia has been demonstrated with thallium perfusion studies, elevated myocardial lactate levels during rapid atrial pacing, and positron emission tomography.
 - b. While epicardial artery obstruction is less common, **mismatch of supply and demand** due to thickened vessels and small vessel disease from increased collagen deposition in the intima and media are the most likely pathophysiologies of ischemia. Contributing factors include the following:
 - (1) Small vessel coronary disease with decreased vasodilator capacity
 - (2) Elevated myocardial wall tension as a consequence of delayed diastolic relaxation time and obstruction to LV outflow
 - (3) Decreased capillary-to-myocardial fiber ratio
 - (4) Decreased coronary perfusion pressure
- 3. **Syncope and presyncope** are usually a consequence of diminished cerebral perfusion caused by inadequate cardiac output. These episodes are commonly associated with exertion or cardiac arrhythmia.
- 4. **Sudden death.** The annual mortality rate for HCM is **1%**. Most deaths are sudden or unexpected.
 - a. Not all patients with HCM are at equal **risk for sudden death**. Twenty-two percent of patients with sudden death have no symptoms. **Sudden death appears to be most common among older children and young adults**; it is rare in the first decade of life. Approximately 60% of deaths occur during periods of inactivity; the remaining deaths occur after vigorous physical exertion.
 - b. **Arrhythmogenic and ischemic mechanisms** can initiate a clinical spiral of hypotension, decreased diastolic filling time, and increased outflow obstruction that often culminates in death.

III. PHYSICAL EXAMINATION

A. Inspection of the jugular venous system may reveal a prominent *a* wave that indicates hypertrophy and lack of compliance of the right ventricle. A precordial heave, representing right ventricular (RV) strain, can be found in persons with concomitant pulmonary hypertension.

B. Palpation

1. The **apical precordial pulse is usually laterally displaced and diffuse**. LV hypertrophy may cause a presystolic apical impulse or palpable fourth heart sound (S_4). A three-component apical impulse may occur, with the third impulse resulting from a late systolic bulge of the left ventricle.
2. The carotid pulse has been classically described as bifid. This **rapid carotid upstroke followed by a second peak** is caused by a hyperdynamic left ventricle. This is in contrast to the *parvus et tardus* pulse of fixed aortic or subvalvular aortic stenosis, which is a carotid pulse characterized by a delayed amplitude and upstroke.

C. Auscultation

1. S_1 (first heart sound) is usually normal and is preceded by S_4 .
2. S_2 (second heart sound) can be normal or paradoxically split as the result of the prolonged ejection time of patients with severe outflow obstruction.
3. The **harsh, crescendo–decrescendo systolic murmur** associated with HCM is best heard at the left sternal border. It radiates to the lower sternal border but not to the neck vessels or axilla.
 - a. An important aspect of the murmur is its **variation in intensity and duration** with ventricular loading conditions. During periods of increased venous return, the murmur is of shorter duration and is less intense. In the underfilled ventricle and during periods of increased contractility, the murmur is harsh and of a longer duration.
 - (1) The **concomitant murmur of mitral insufficiency** can be differentiated because of its holosystolic, blowing quality that radiates to the axilla.
 - (2) A soft, early, decrescendo, **diastolic murmur of aortic insufficiency** is found in approximately 10% of patients with HCM.
 - b. **Maneuvers that affect preload and afterload** can be helpful in diagnosing HCM and differentiating it from other systolic murmurs (Table 10.2).

TABLE 10.2

Effects of Maneuvers or Pharmacologic Intervention to Differentiate Murmur of Hypertrophic Cardiomyopathy from Aortic Stenosis

Maneuver	Physiologic effect	HCM	AS	MR
Valsalva and standing	Decreases VR, SVR, and CO	↑	↓	↓
Squat and handgrip	Increases VR, SVR, and CO	↓	↑	↑
Amyl nitrite	Increases VR Decreases SVR and LV volume	↑	↑	↓
Phenylephrine	Increases SVR and VR	↓	↑	↑
Extrasystole	Decreased LV volume	↑	↓	No change
Post-Valsalva release	Increased LV volume	↓	↑	No change

AS, aortic stenosis; CO, cardiac output; HCM, hypertrophic cardiomyopathy; LV, left ventricular; MR, mitral regurgitation; SVR, systemic vascular resistance; VR, venous return; ↓, decrease; ↑, increase.

TABLE 10.3 Molecular Genetics of Hypertrophic Cardiomyopathy

Gene symbol	Protein name	% of HCM caused by mutations in this gene
<i>MYH7</i>	Myosin heavy chain	40
<i>MYBPC3</i>	Myosin-binding protein C	40
<i>TNNT2</i>	Troponin T	5
<i>TNNI3</i>	Troponin I	5
<i>TPM1</i>	Tropomyosin 1	2
<i>ACTC1</i>	Actin, α	Unknown
<i>MYL2</i>	Myosin regulatory light chain 2	Unknown
<i>MYL3</i>	Myosin light polypeptide 3	1

HCM, hypertrophic cardiomyopathy.

IV. GENETIC ASPECTS OF HCM. Familial HCM is caused by mutation in one of the genes currently known to encode different components of sarcomere proteins or sarcomere-associated proteins that are inherited in an autosomal dominant manner (see Chapter 42). To date, familial HCM is known to be caused by over 1,400 different mutations in at least 8 genes (Table 10.3). Multiple analyses suggest that these common genetic subtypes are essentially phenotypically indistinguishable.

HCM genotype does not necessarily imply that subjects will have the phenotypic traits of HCM as variable penetrance exists, and environmental factors as well as modifier genes affect whether a particular subject will manifest HCM phenotypically.

Patients with an **identified pathogenic mutation** are at an increased risk for cardiovascular death, nonfatal stroke, or progression to NYHA functional class III or IV compared with patients with no identified mutations.

V. DIAGNOSTIC TESTING

A. Electrocardiogram (ECG). Although most patients have electrocardiographic evidence of disease, no changes are pathognomonic for HCM. Common electrocardiographic findings in HCM are listed in Table 10.4. These abnormalities do not correlate with disease severity or pattern of hypertrophy.

B. Echocardiography is the preferred diagnostic method because of its high sensitivity and low risk profile. It also allows characterization of the site of obstruction. Careful

TABLE 10.4 Electrocardiographic Findings in Hypertrophic Cardiomyopathy

Evidence of right and left atrial enlargement
Q waves in the inferolateral leads
Voltage criteria for large negative precordial T waves (associated with Japanese variant)
Left-axis deviation
Short PR interval with slurred upstroke

TABLE 10.5 Two-Dimensional, M-Mode, and Doppler Echocardiographic Findings in Hypertrophic Cardiomyopathy

Asymmetric septal hypertrophy (> 13 mm)
Systolic anterior motion of the mitral valve
Small left ventricular cavity
Septal immobility
Premature closure of the aortic valve
Resting gradients > 30 mm Hg
Provocable gradients > 50 mm Hg
Normal or increased motion of the posterior wall
Reduced rate of closure of the mitral valve in mid-diastole
Mitral valve prolapse with regurgitation
Maximal left ventricular diastolic wall thickness > 15 mm

assessment for conditions that can also cause secondary hypertrophy (aortic or sub-aortic stenosis, hypertension, infiltrative diseases, etc.) should also be done.

1. **M-mode and two-dimensional** echocardiographic findings in HCM are listed in Table 10.5. Close evaluation of the extent of hypertrophy should be done given the role of septal thickness in risk stratification for sudden cardiac death (SCD).
2. **Doppler echocardiography** enables recognition and quantification of dynamic LVOT obstruction as well as the response to various maneuvers.
 - a. Approximately one-fourth of patients with HCM have a resting pressure gradient between the body and LVOT; others have only provocable gradients.
 - b. The **diagnosis of HCM with obstruction** is based on resting peak instantaneous gradient > 30 mm Hg. These gradients correlate directly with the time of onset and duration of contact between the mitral leaflet and the septum, as occurs during SAM of the mitral leaflet. The earlier and longer the contact occurs, the higher the pressure gradient.
 - (1) Inducing obstruction and, therefore, gradients, in patients believed to have latent obstruction, can be accomplished with substances (e.g., amyl nitrite, isoproterenol, and dobutamine) or maneuvers (e.g., Valsalva maneuver and exercise) that decrease LV preload or increase contractility.
 - (2) Although the **clinical relevance of outflow obstruction has been debated, relief by means of surgical or pharmacologic technique is associated with clinical improvement** among many patients. Echocardiographic recognition of HCM and of HCM with outflow obstruction is, therefore, important.
 - c. **Recognition of mitral regurgitation (MR).** Echocardiographic evaluation of MR and the detection of valve anomalies may have a considerable effect on medical and surgical strategies in the care of patients with HCM.
 - (1) Approximately **60% of patients with HCM have structural abnormalities of the mitral valve**, including increased leaflet area, elongation of leaflets, and anomalous insertion of papillary muscles directly into the anterior mitral leaflet.

(2) When there is no leaflet abnormality, the degree of MR is directly related to the severity of obstruction and lack of leaflet coaptation.

C. Magnetic resonance imaging (MRI). Advantages of MRI in the evaluation of HCM include excellent resolution, lack of radiation, inherent contrast, three-dimensional imaging, and tissue characterization. Disadvantages are cost, length of study, and exclusion of patients with contraindications to exposure to magnetism, such as patients with implantable cardioverter–defibrillators (ICDs) or pacemakers.

1. MRI can detect **LV hypertrophy** missed by echocardiography, specifically in the anterolateral and basal LV free walls.
2. **Myocardial scar**, often found in patients with HCM, can be detected as **delayed hyperenhancement with gadolinium-contrast MRI**. Some small studies have suggested that the amount of hyperenhancement may be a predictor of SCD in this patient population.
3. Improved identification of MR, SAM, abnormal papillary muscles, and diastolic dysfunction.
4. Differentiate from alternative causes of LV thickening such as Fabry disease and amyloidosis.

D. Cardiac catheterization is used primarily for defining coronary anatomy before myectomy or a mitral valve operation and evaluation of ischemic symptoms. The characteristic findings of HCM during hemodynamic assessment are listed in Table 10.6 and illustrated in Figure 10.1.

1. Patients with normal coronary arteries may have **typical ischemic symptoms**. These symptoms may indicate myocardial bridges, phasic narrowing during systole, reduced coronary flow reserve, or systolic reversal of flow in the epicardial vessels.
2. **Left ventriculography** usually reveals a hypertrophied ventricle, prominent septal bulge, nearly complete obliteration of the ventricular cavity during systole, SAM, and MR. The **spadelike** appearance of the ventricular cavity is confined to ventricles with **apical involvement**.

VI. MANAGEMENT STRATEGIES

A. Priority of therapy. Effective therapy must include pathways for the **prevention and management of heart failure** caused by diastolic and systolic dysfunction, arrhythmias, ischemia, and failed medical therapy and the **prevention of sudden death**. The specific strategies for patients with HCM can be as heterogeneous as the clinical presentation and evolution. See Figure 10.2 for a simplified treatment algorithm.

TABLE 10.6 Hemodynamic Findings during Cardiac Catheterization

Subaortic or mid-ventricular outflow gradient on catheter pullback
Spike-and-dome pattern of aortic pressure tracing ^a
Elevated right and left ventricular end-diastolic pressures
Elevated pulmonary capillary wedge pressure
Increased V wave on wedge tracing ^b
Elevated pulmonary arterial pressure

^aA consequence of outlet obstruction.

^bMay result from either mitral regurgitation or elevated left atrial pressure.

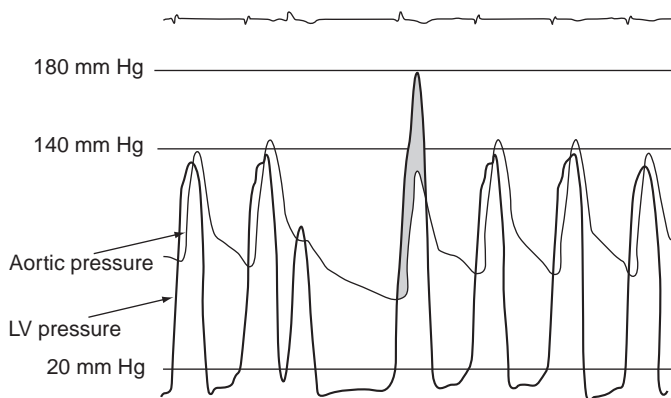


FIGURE 10.1 Severe increase in the left ventricular (LV) aortic gradient in the beat after a premature ventricular contraction (PVC) (Brockenbrough-Braunwald-Morrow sign) due to an increase in contractility and decrease in afterload during the post-PVC beat.

B. Medical therapy. Although never proven to reduce mortality in clinical trials, **β -blockers are the first-line therapy** for HCM, regardless of the presence of LV outflow obstruction.

1. **β -Blockers** improve symptoms and exercise tolerance. β -Blockers with additional α -blocking properties, such as carvedilol and labetalol, should probably not be used as first-line agents because of their additional vasodilatory properties.
 - a. The mechanism of action of β -blockers is inhibition of sympathetic stimulation brought about by the negative inotropic and chronotropic properties of the drugs. β -Blockers diminish myocardial oxygen requirements and augment diastolic filling, which mitigate angina and the detrimental effects of LV outflow obstruction, respectively.
2. **Calcium channel blockers (CCBs)** are considered to be second-line agents that are also effective in reducing the common symptoms of HCM in patients who are intolerant of or have undergone unsuccessful treatment with β -blockers.
 - a. **CCBs** have a negative inotropic effect and reduce the heart rate and blood pressure. They may also have beneficial effects on diastolic function by improving rapid diastolic filling, although possibly at the expense of higher LV end-diastolic pressures. The beneficial effects seem to be limited to the nondihydropyridines **verapamil** and **diltiazem** (Table 10.7). Conversely, dihydropyridine CCBs may be contraindicated (see below).
 - b. Because of the unpredictable hemodynamic effects of their vasodilator properties, CCBs should be administered cautiously to patients with considerable outlet obstruction and elevated pulmonary pressures.
3. **Disopyramide**, a class 1a antiarrhythmic agent, may be an effective alternative or adjunct to β -blocker and CCB therapy. Its strong negative inotropic qualities coupled with its ability to suppress ventricular and supraventricular arrhythmias make it an effective treatment when marked outflow obstruction or arrhythmias are manifested. Potential disadvantages are anticholinergic properties, accumulation in patients with hepatic or renal dysfunction, the possibility of augmenting atrioventricular (AV) nodal conduction in the presence of atrial fibrillation, and

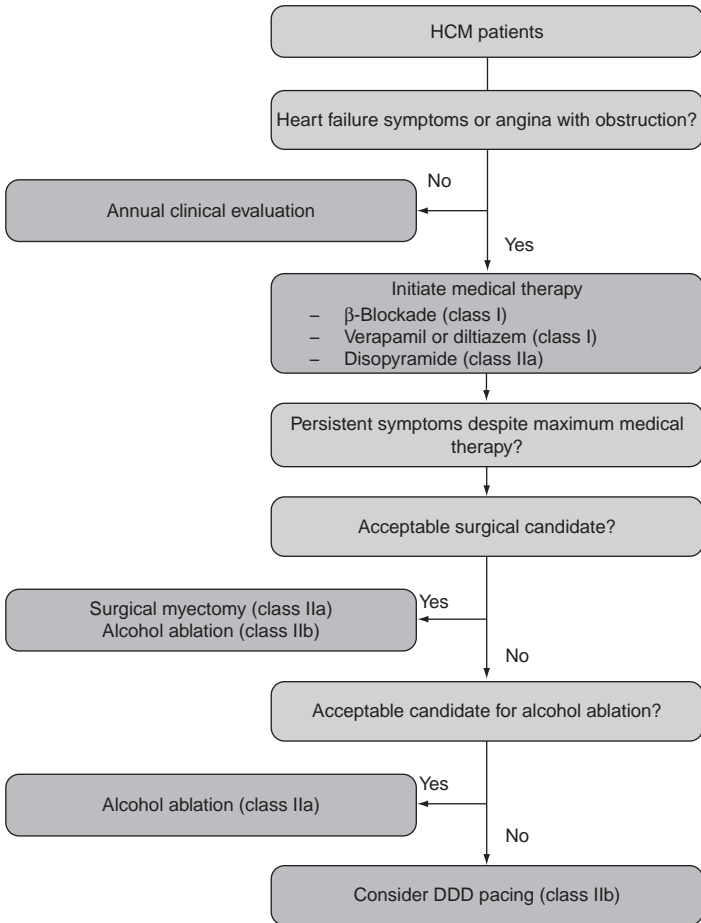


FIGURE 10.2 Management algorithm for hypertrophy cardiomyopathy. DDD, dual pacing for both chambers, dual chamber activity sensing, and dual response; HCM, hypertrophic cardiomyopathy. (Adapted from Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *Circulation* 2011;124:e783–e831)

waning hemodynamic effects with time. It is because of these significant side effects that disopyramide is typically used in a very symptomatic patient when a more definitive procedure is being planned, such as surgical myectomy or alcohol septal ablation. It is not considered to be a long-term treatment for HCM.

4. **Dihydropyridine CCBs** (e.g., nifedipine and amlodipine), **angiotensin-converting enzyme inhibitors**, and **angiotensin receptor blockers** should be avoided because they cause peripheral vasodilation, which may result in decreased LV filling and worsening of outflow tract obstruction.

TABLE 10.7 Pharmacologic Therapy for Hypertrophic Cardiomyopathy

Drug	Standard dose ^a (mg/d)
β-Blockers	
Metoprolol	50–200
Atenolol	50–100
Calcium channel antagonists	
Verapamil	120–360
Diltiazem	120–360
Antiarrhythmics	
Disopyramide	400–1,200
Amiodarone	200–400
Sotalol	160–320

^aDoses can be increased to treat patients with persistent symptoms who have no evidence of an adverse response.

5. **Diuretics** should be used cautiously as high filling pressures are often necessary due to the stiff ventricle, and overdiuresis may reduce LV size and increase obstruction.
 6. **Digoxin** should be avoided due to potential worsening of the LVOT obstruction secondary to the positive inotropic effect.
 7. **Phenylephrine**, a pure α -agonist that causes vasoconstriction, can be considered in cases of refractory hypotension unresponsive to IV fluids. Pressors with positive inotropic effects, such as norepinephrine, dopamine, and dobutamine, can provoke LVOT obstruction and should be avoided.
- C. **Nonpharmacologic treatment** is typically reserved for those patients with symptoms despite optimal medical therapy (Table 10.8). With severe symptomatic, nonobstructive HCM, cardiac transplantation remains the only option. However, persons with symptomatic obstruction and resting or latent gradient of 50 mm Hg or more despite optimal medical treatment are candidates for septal myectomy or alcohol septal ablation. Younger patients with gradients > 75 mm Hg and low surgical risk should be considered for septal myectomy even in the absence of symptoms.
1. **Septal myectomy** of HCM has been performed for more than 50 years and is the **procedure of choice for patients with progressive, drug-refractory functional limitation due to LVOT obstruction**.
 - a. When performed by an experienced surgeon, septal myectomy is considered the most definitive treatment and is associated with a mortality rate of < 1% to 2%. It is effective in abolishing resting gradients in > 90% of patients, and most patients have long-lasting symptomatic relief. Enlargement of the LVOT has been found to reduce SAM, MR, LV systolic and end-diastolic pressures, left atrial pressure, and resting gradients. A retrospective study by Ommen et al. (1) from the Mayo Clinic published in 2005 demonstrated that patients who underwent myectomy had significantly longer survival and less incidence of SCD as compared with patients with obstruction who did not undergo surgery. In fact, after myectomy, survival was no different as compared with HCM patients who did not have obstruction at baseline.

TABLE 10.8 Excerpts from 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy

Invasive therapies—recommendations

Class I

Septal reduction therapy should be performed only by experienced operators in the context of a comprehensive HCM clinical program and only for the treatment of eligible patients with severe drug-refractory symptoms and LVOT obstruction.

Class IIa

Consultation with centers experienced in performing both surgical septal myectomy and alcohol septal ablation is reasonable when discussing treatment options for eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: C)*

Surgical septal myectomy, when performed in experienced centers, can be beneficial and is the first consideration for the majority of eligible patients with HCM with severe drug-refractory symptoms and LVOT obstruction. *(Level of Evidence: B)*

Surgical septal myectomy, when performed at experienced centers, can be beneficial in symptomatic children with HCM and severe resting obstruction (> 50 mm Hg) for whom standard medical therapy has failed. *(Level of Evidence: C)*

When surgery is contraindicated or the risk is considered unacceptable because of serious comorbidities or advanced age, alcohol septal ablation, when performed in experienced centers, can be beneficial in eligible adult patients with HCM with LVOT obstruction and severe drug-refractory symptoms (usually NYHA functional class III or IV). *(Level of Evidence: B)*

Class IIb

Alcohol septal ablation, when performed in experienced centers, may be considered as an alternative to surgical myectomy for eligible adult patients with HCM with severe drug-refractory symptoms and LVOT obstruction when, after a balanced and thorough discussion, the patient expresses a preference for septal ablation. *(Level of Evidence: B)*

The effectiveness of alcohol septal ablation is uncertain in patients with HCM with marked (i.e., > 30 mm) septal hypertrophy, and therefore the procedure is generally discouraged in such patients. *(Level of Evidence: C)*

Selection of patients for ICD

Class I

The decision to place an ICD in patients with HCM should include application of individual clinical judgment, as well as a thorough discussion of the strength of evidence, benefits, and risks to allow the informed patient's active participation in decision making. *(Level of Evidence: C)*

ICD placement is recommended for patients with HCM with prior documented cardiac arrest, ventricular fibrillation, or hemodynamically significant VT. *(Level of Evidence: C)*

Class IIa

It is reasonable to recommend an ICD for patients with HCM with

1. Sudden death presumably caused by HCM in one or more first-degree relatives. *(Level of Evidence: C)*
2. A maximum LV wall thickness ≥ 30 mm. *(Level of Evidence: C)*
3. One or more recent, unexplained syncopal episodes. *(Level of Evidence: C)*

(Continued)

TABLE 10.8 Excerpts from 2011 ACC/AHA Guidelines for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy (*Continued*)

An ICD can be useful in select patients with NSVT (particularly those < 30 years of age) in the presence of other SCD risk factors or modifiers. (*Level of Evidence: C*)

An ICD can be useful in select patients with HCM with an abnormal blood pressure response with exercise in the presence of other SCD risk factors or modifiers. (*Level of Evidence: C*)

It is reasonable to recommend an ICD for high-risk children with HCM, based on unexplained syncope, massive LV hypertrophy, or family history of SCD, after taking into account the relatively high complication rate of long-term ICD implantation. (*Level of Evidence: C*)

Class IIb

The usefulness of an ICD is uncertain in patients with HCM with isolated bursts of NSVT in the absence of any other SCD risk factors or modifiers. (*Level of Evidence: C*)

The usefulness of an ICD is uncertain in patients with HCM with an abnormal blood pressure response with exercise when in the absence of any other SCD risk factors or modifiers, particularly in the presence of significant outflow obstruction. (*Level of Evidence: C*)

Participation in competitive or recreational sports and physical activity

Class IIa

It is reasonable for patients with HCM to participate in low-intensity competitive sports (e.g., golf and bowling). (*Level of Evidence: C*)

Management of AF

Class I

Anticoagulation with vitamin K antagonists (i.e., warfarin, to an INR of 2.0 to 3.0) is indicated in patients with paroxysmal, persistent, or chronic AF and HCM. (*Level of Evidence: C*)

Ventricular rate control in patients with HCM with AF is indicated for rapid ventricular rates and can require high doses of β -antagonists and nondihydropyridine calcium channel blockers. (*Level of Evidence: C*)

Class IIa

Disopyramide (with ventricular rate-controlling agents) and amiodarone are reasonable antiarrhythmic agents for AF in patients with HCM. (*Level of Evidence: C*)

Radiofrequency ablation for AF can be beneficial in patients with HCM who have refractory symptoms or who are unable to take antiarrhythmic drugs. (*Level of Evidence: B*)

Maze procedure with closure of LA appendage is reasonable in patients with HCM with a history of AF, either during septal myectomy or as an isolated procedure in selected patients. (*Level of Evidence: C*)

Class IIb

Sotalol, dofetilide, and dronedarone might be considered alternative antiarrhythmic agents in patients with HCM, especially in those with an ICD, but clinical experience is limited. (*Level of Evidence: C*)

AF, atrial fibrillation; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; INR, international normalized ratio; LA, left atrial; LV, left ventricular; LVOT, left ventricular outflow tract; NSVT, nonsustained ventricular tachycardia; SCD, sudden cardiac death; VT, ventricular tachycardia. From Gersh BJ, Maron BJ, Bonow RO, et al. 2011 ACCF/AHA Guideline for the Diagnosis and Treatment of Hypertrophic Cardiomyopathy. *Circulation* 2011;124:e783–e831.

2. **Alcohol septal ablation**—essentially a controlled infarction of the septum—is an alternative to septal myectomy. Because it has a greater risk than myectomy of complications including complete heart block and extensive myocardial infarction, it is **generally used in patients who are not candidates for surgical myectomy**. There are no randomized trials comparing myectomy and septal ablation.
 - a. **Technique.** In the cardiac catheterization laboratory, a guidewire is advanced through the left main trunk to probe the first or second septal perforator, or both. An angioplasty catheter is placed in the proximal portion of the septal branch for vessel isolation. Ultrasonic contrast agents are infused in the cannulated perforator to define the area at risk for infarction. Infusion of 1 to 4 mL of absolute alcohol causes infarction in the zone of septal myocardium served by the cannulated septal branch. In most centers, a temporary ventricular pacing catheter is placed into the RV apex before performing the ablation, in order to manage any transient conduction abnormalities.
 - b. **Results.** In the majority of patients, there is a marked immediate decrease in the LVOT gradient. This gradient response is thought to be triphasic: immediate reduction (due to stunning), early reappearance, and sustained fall by 3 months after the procedure (due to remodeling). Within this initial period, most patients attain good symptomatic relief. Risks of the procedure include high-grade AV block, coronary dissection, large anterior wall myocardial infarction, pericarditis, and electrical instability of the scar that forms as a result of the infarction. In a Scandinavian study by Jensen et al. of 313 alcohol septal ablation procedures performed in 279 patients, mortality was low at 0.6%, but 20% of patients required implantation of a pacemaker (2).
3. **Dual-chamber pacing** has been previously used in hopes of alleviating symptoms by altering the timing of septal contraction, but studies have not confirmed any long-term benefit. Dual-chamber pacing should only be considered in patients with medically refractory symptoms who are not candidates for septal reduction therapy.
4. **Special management considerations**
 - a. **Atrial fibrillation**, which occurs in up to a third of patients with HCM, can have devastating consequences. Atrial fibrillation decreases diastolic filling time and causes the loss of atrial systole. These changes can lead to acute hemodynamic decompensation and pulmonary edema given the stiff left ventricle of patients with HCM. Because of the increased risk of thromboembolism, all patients with HCM-associated atrial fibrillation (be it paroxysmal or permanent) should be strongly considered for anticoagulation therapy. Aggressive efforts should be made to maintain sinus rhythm given the increased morbidity and mortality associated with atrial fibrillation in patients with HCM.
 - (1) **Acute paroxysms** of atrial fibrillation are best managed with prompt cardioversion with transesophageal echocardiogram (TEE). Data concerning the prevention of recurrence are lacking, but the 2006 ACC/AHA Guidelines for the Management of Patients with Atrial Fibrillation suggest disopyramide or amiodarone as possible agents. Other class III agents, such as dofetilide, sotalol, and dronedarone, should be reserved for use in patients with an ICD given the paucity of safety data.
 - (2) **Chronic atrial fibrillation** may be well tolerated if the heart rate is controlled with β -blockers or calcium channel antagonists.
 - (3) **Maze or radiofrequency ablation.** For patients who do not tolerate atrial fibrillation and cannot be maintained in sinus rhythm, AV nodal ablation and implantation of a dual-chamber pacemaker may be an option. Other options including catheter ablation or combined surgical myectomy-maze can be considered.

- b. **Risk stratification for sudden death** remains one of the more challenging aspects for the management of HCM, especially for primary prevention. Table 10.9 lists the established factors for risk stratification. Additional risk factors (e.g., scar burden as determined by late gadolinium contrast on MRI) continue to be evaluated. Currently, the only effective means of preventing SCD is an ICD.
- (1) Placement of an ICD carries several potential complications, including but not limited to infection, inappropriate firing, lead fracture, and generator depletion. The **decision to implant an ICD is highly individualized** and should take into consideration that younger patients will be subject to a higher risk of device-related complications due to the longer time the device will be present.
 - (2) Patients who survive an episode that might have ended in sudden death, have sustained ventricular arrhythmias, or have multiple risk factors for sudden death should be strongly considered for an ICD.
 - (3) Selection of patients for ICD implantation as primary prevention is difficult. A retrospective multicenter study from the Minneapolis Heart Institute Foundation (3) evaluated the incidence of appropriate ICD interventions in patients with HCM who previously received a device for one of four SCD risk factors: history of HCM-related SCD in a relative younger than 50 years, “massive” LV hypertrophy, nonsustained ventricular tachycardia on Holter monitoring, and prior unexplained syncope (nonneurocardiogenic). The study concluded that one risk factor may be enough for consideration of ICD implantation. Of note, there was no control group in this study.

VII. SPECIAL CONSIDERATIONS

A. Athlete's heart

1. **Differentiating HCM from hypertrophy of athletes.** Failure to diagnose HCM places an athlete at undue risk for sudden death while incorrect labeling of HCM often leads to irrational treatments, unnecessary fears, and inappropriate recommendations concerning exercise. Diagnostic uncertainty is greatest when maximal diastolic LV wall thickness exceeds the upper limit of normal (12 mm) but is less than the defined lower limit of expected hypertrophy (15 mm) for HCM and in the absence of SAM and LV outflow obstruction.
 - a. Characteristics that **substantiate the diagnosis of HCM** include unusual patterns of hypertrophy, an LV end-diastolic diameter of < 45 mm, septal thickening > 15 mm, left atrial enlargement, abnormal diastolic function, family history of HCM, and abnormal LV filling.

TABLE 10.9 Risk Factors for Sudden Cardiac Death

Previous cardiac arrest
Sustained ventricular tachycardia
Prolonged or repetitive episodes of nonsustained ventricular tachycardia on Holter monitor
Left ventricular wall thickness > 30 mm
Family history of SCD
No change or a decrease in blood pressure with exercise
Syncope or near-syncope

SCD, sudden cardiac death.

- b. Findings more consistent with the **hypertrophied heart of an athlete** are LV end-diastolic diameter > 45 mm, septal thickening < 15 mm, left atrial size < 4 cm, LV end-diastolic diameter > 45 mm, and a decrease in LV thickness with deconditioning.

Should differentiation not be possible, the patient should stop training: after several months, ventricular hypertrophy will typically regress in the athlete but will persist in a patient with HCM.

- 2. **Participation in sports.** HCM is the most common cause of sudden death in young athletes. It appears that intense exercise, with its resulting rapid changes in hemodynamics, can increase the risk of death as well. The European Society of Cardiology recommends prohibiting athletes with HCM from participating in competitive high school and college sports. These recommendations remain in force after medical or surgical intervention.
 - a. Athletes with HCM with or without obstruction who are younger than 30 years should **not** participate in competitive, aerobically demanding sports.
 - b. Participation in recreational sports should take into consideration the intensity of the activity (with the resulting fluctuations in hemodynamics) and the danger to the individual should impaired consciousness occur. For instance, activities such as rock climbing and weightlifting carry a higher risk of morbidity and mortality than activities such as golf and bowling.

B. Infective endocarditis (IE)

- 1. **Predisposing factors.** Gastrointestinal and genitourinary tract surgical procedures place patients at increased risk for bacteremia. It is unclear if dental procedures place patients with HCM at risk.
- 2. **Pathophysiology.** Bacterial seeding of endomyocardial lesions is caused by repeated trauma associated with hemodynamic and intrinsic valvular abnormalities.
- 3. **Prophylaxis.** Guidelines on the prevention of IE published by the AHA in 2007 question the practice of treating patients with HCM with antibiotics prior to dental procedures and recommend against it except in the setting of prior endocarditis. However, there are no large, prospective, randomized double-blind trials testing the efficacy of IE prophylaxis. Given the catastrophic consequences of endocarditis in patients with HCM, routine antimicrobial prophylaxis for IE should be weighed on an individual basis.

C. Yamaguchi's or Apical HCM

- 1. **Clinical presentation.** Patients experience chest pain, dyspnea, fatigue, and, in rare instances, sudden death.
- 2. **Prevalence.** Within Japan, apical HCM constitutes 25% of all cases of HCM. Outside Japan, only 1% to 2% of cases are associated with isolated apical hypertrophy.
- 3. **Diagnostic testing**
 - a. An **ECG** reveals giant negative T waves in the precordial leads and LV hypertrophy (Fig. 10.3).
 - b. **Echocardiographic findings include the following:**
 - (1) Localized hypertrophy in the distal left ventricle beyond the origin of the chordae tendineae
 - (2) Wall thickness in the apical region of at least 15 mm or a ratio of maximal apical to posterobasal thickness > 1.5
 - (3) Exclusion of hypertrophy in other parts of the ventricular wall
 - (4) No LVOT obstruction or gradient
 - c. **MRI** demonstrates localized hypertrophy to the cardiac apex. MRI is useful in the care of patients with poor echocardiographic windows.
 - d. **Cardiac catheterization** reveals a spadelike configuration of the LV cavity at end diastole and apical end-systolic LV cavity obliteration.

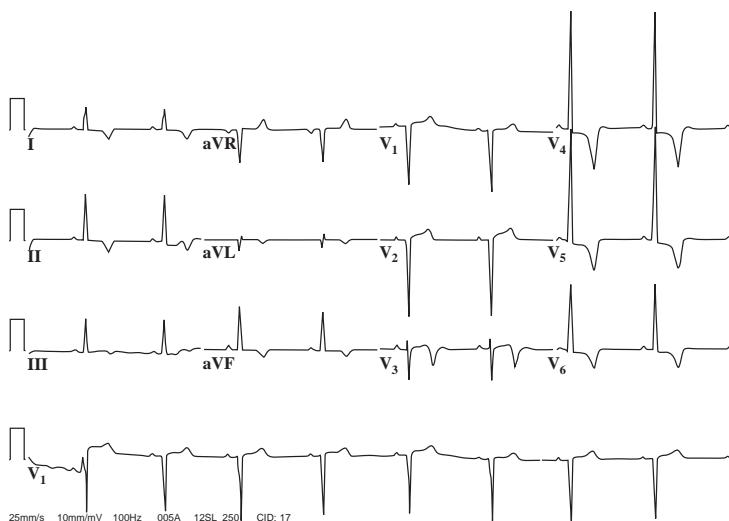


FIGURE 10.3 Electrocardiogram (ECG) in an apical hypertrophic cardiomyopathy (HCM, Yamaguchi). The classic ECG for apical HCM has deep anteroapical T-wave inversions.

4. **Prognosis** is favorable compared with that associated with other forms of HCM.
 5. **Therapy.** Therapeutic efforts are limited to management of diastolic dysfunction with β -blockers and calcium channel antagonists.
- D. HCM among the elderly**
1. **Clinical presentation.** In addition to the signs and symptoms of other forms of HCM, hypertension is more common with HCM in the elderly population.
 2. **Incidence.** Although the incidence is unknown, HCM among the elderly is probably more common than expected.
 3. **Genetic aspects.** Reports have suggested that the delayed expression of mutations in the gene for cardiac myosin-binding protein C may play an important role in HCM in the elderly.
 4. **Echocardiographic findings** for elderly patients (65 years or older) are compared with findings for young patients (40 years or younger) as follows:
 - a. **Common findings**
 - (1) LVOT gradient, both provokable and at rest
 - (2) Asymmetric hypertrophy
 - (3) SAM of the mitral valve
 - b. **Differences pertaining to the elderly**
 - (1) Less hypertrophy
 - (2) Less RV involvement
 - (3) Ovoid versus crescentic left ventricle
 - (4) Prominent septal bulge (i.e., sigmoid septum)
 - (5) More acute angle between the aorta and septum as the aorta uncoils with age
 - (6) Management of HCM in the elderly is similar to that of other forms of HCM.
 - (7) The **prognosis** is favorable compared with that for forms of HCM that occur at a younger age.

- E. Screening of family members.** With familial HCM, the dominant pattern of inheritance imparts a 50% chance of disease transmission to offspring.
- Serial 12-lead ECG and transthoracic echocardiogram are recommended **every 12 to 18 months in first-degree relatives** of HCM patients starting at age 12 during adolescence due to the propensity of HCM to worsen during growth spurts.
 - Because of the possibility of late-onset phenotypic expression, **screening of first-degree relatives should continue into middle age**, but the frequency of screening can be scaled back to a minimum of every 5 years once full growth has been obtained.
 - If genetic testing reveals a mutant HCM gene in the offspring, the high penetrance of the mutation imparts a > 95% lifetime risk of developing clinical and/or phenotypic evidence of disease. These gene-positive offspring should continue with serial examinations.
 - First-degree relatives that are mutation negative have no risk of developing HCM and do not need further screening.

ACKNOWLEDGMENTS: *The author acknowledges the contributions of Eiran Gordeski, MD; Mark Robbins, MD; and A. Thomas McRae III, MD, to prior editions of this chapter.*

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Myocarditis

I. INTRODUCTION. Myocarditis is defined as an inflammatory infiltration of the myocardium with associated necrosis or degeneration, or both. The disease is also known as **inflammatory cardiomyopathy** (or myocarditis with cardiac dysfunction in the World Health Organization 1995 classification for cardiomyopathy). The incidence and prevalence of myocarditis are unclear; the syndrome is underdiagnosed because of the large number of asymptomatic cases. Myocarditis usually affects younger individuals; the median age of patients with lymphocytic myocarditis is 42 years.

A. Clinicopathologic classification of myocarditis is clinically oriented but not widely used.

1. **Fulminant myocarditis** (17%) usually has a distinct onset. It can result in either complete, spontaneous resolution or rapidly progressive deterioration and death due to severe cardiac compromise. Usually there are multiple active foci of inflammatory infiltrate on histology with complete resolution.
2. **Acute myocarditis** (65% of myocarditis cases) has an indistinct onset, with moderate cardiovascular compromise and incomplete recovery, often resulting in cardiac dysfunction or subsequent death. Histologically, there are active or borderline inflammatory infiltrates that resolve completely over time.
3. **Chronic active myocarditis** (11% of myocarditis cases) has a presentation similar to that of acute myocarditis, but the chronic form usually progresses to only mild or moderate cardiac dysfunction, occasionally with restrictive physiology. Histologic examination often shows ongoing fibrosis, suggesting chronic inflammatory changes.
4. **Chronic persistent myocarditis** (7% of myocarditis cases) has an indistinct onset, with nonresolving active or borderline inflammatory infiltrates seen on histologic examination. Usually, there is no cardiovascular compromise.

B. Histologic classification of myocarditis, also called the Dallas classification (1986)

1. Initial biopsy
 - a. Myocarditis: myocardial necrosis or degeneration, or both, in the absence of significant coronary artery disease with adjacent inflammatory infiltrates or fibrosis, or both
 - b. Borderline myocarditis: inflammatory infiltrates too sparse or myocyte damage not apparent
 - c. No myocarditis: no inflammatory infiltrates or myocyte damage
2. Subsequent biopsy
 - a. Ongoing (persistent) myocarditis or fibrosis, or both
 - b. Resolving (healing) myocarditis or fibrosis, or both
 - c. Resolved (healed) myocarditis or fibrosis, or both

C. World Health Organization (Marburg Criteria, 1996). A minimum of 14 infiltrating leukocytes per mm (1), preferably T lymphocytes, and up to 4 macrophages may be included.

II. CLINICAL PRESENTATION

A. Signs and symptoms

1. Myocarditis can be **totally asymptomatic** or can manifest with **chest pain syndromes** ranging from mild persistent chest pain of acute myopericarditis (35% of cases) to severe symptoms that mimic acute myocardial infarction. Chest pain associated with coronary artery vasospasm may rarely occur in patients with myocarditis. Alternatively, chest pain may be more typical for pericarditis, suggesting pericardial involvement.
2. About 60% of patients may have antecedent arthralgias, malaise, fever, sweats, or chills consistent with viral infections (e.g., pharyngitis, tonsillitis, and upper respiratory tract infection) 1 to 2 weeks before onset.
3. The hallmark symptoms are those of **heart failure** (e.g., dyspnea, fatigue, and edema). In many patients who develop heart failure, fatigue and decreased exercise capacity are the initial manifestations. However, diffuse, severe myocarditis can progress rapidly and result in acute myocardial failure and cardiogenic shock. The diagnosis is usually presumptive, based on patient demographics and the clinical course (i.e., spontaneous recovery after supportive care).
4. In some instances, patients may present with **arrhythmia** in the form of syncope, palpitations caused by heart block (i.e., Stokes-Adams attack), ventricular tachyarrhythmia, or even sudden cardiac death. Sinus tachycardia is more frequent than serious atrial or ventricular arrhythmias. Palpitations secondary to premature atrial or ventricular extrasystoles are common.

B. Physical findings. Patients often present with signs of **acute decompensated heart failure**, including an S_3 (third heart sound) gallop, central and peripheral edema, jugular venous distention, and tachycardia (see Chapter 8). An audible pericardial friction rub may accompany concomitant myopericarditis. Specific findings in special cases are as follows:

1. **Sarcoid myocarditis:** lymphadenopathy, also with arrhythmias, and sarcoid involvement in other organs (up to 70%)
2. **Acute rheumatic fever** (usually affects heart in 50% to 90%): associated signs such as erythema marginatum, polyarthralgia, chorea, and subcutaneous nodules (i.e., Jones criteria)
3. **Hypersensitive or eosinophilic myocarditis:** pruritic maculopapular rash and history of onset temporally related to initiation of potential culprit medications
4. **Giant cell myocarditis (GCM):** sustained ventricular tachycardia in rapidly progressive heart failure
5. **Peripartum cardiomyopathy:** heart failure developing in the last month of pregnancy or within 5 months after delivery (see Chapter 38)

III. LABORATORY EVALUATION

A. Inflammatory markers of myocarditis

1. **Complete blood count.** Leukocytosis is common (often lymphocytic), although the presence of eosinophilia may suggest hypersensitive (eosinophilic) myocarditis.
2. **Elevated acute phase reactants** such as erythrocyte sedimentation rates or ultrasensitive C-reactive protein are good monitors of clinical progression or response to therapy, but they have **low specificity** for myocarditis. Novel inflammatory markers under investigation include tumor necrosis factor- α , interleukins, interferon- γ , serum-soluble Fas, and soluble Fas ligand levels. Elevation of these markers portends a worse prognosis.
3. **Serum viral antibody titers** are usually increased fourfold or more acutely and gradually fall during convalescence. However, measurement of viral antibody titers is rarely indicated.
4. **Anticardiac antibody titers.** Because of their low specificity, measurement of anticardiac antibody titers (against sarcolemma, myosin, laminin, ADP/ATP

translocator, or β -adrenergic receptors) is not indicated (only 62% of myocarditis cases have titers $\geq 1:40$).

- B. Rheumatologic screening.** Screening of antinuclear antibodies and rheumatoid factor is often indicated. Disease-specific testing is indicated if the following conditions are suspected:
 1. Systemic lupus erythematosus: anti-dsDNA (reported positive anti-Ro/SSA and anti-La/SSB in lupus carditis in children)
 2. Polymyositis: anti-Jo₁
 3. Wegener's granulomatosis: c-ANCA (antineutrophil cytoplasmic antibody)
 4. Scleroderma: anti-Scl₇₀
- C. Serum cardiac enzymes** (markers of myonecrosis): creatinine kinase (myoglobin subfraction) is elevated in only 7.5% of patients with biopsy-proven myocarditis, whereas the cardiac **troponin I or T is elevated in at least 50% of patients** with biopsy-proven myocarditis (89% to 94% specificity and 34% to 53% sensitivity).

IV. DIAGNOSTIC TESTING

- A. Electrocardiogram.** The electrocardiogram often reveals sinus tachycardia, although the presence of nonspecific ST-segment and T-wave abnormalities may represent focal or global ischemia. Occasionally, the changes in electrocardiogram are suggestive of an acute myocardial infarction and may include ST-segment elevation. Pericarditis can accompany myocarditis and is often manifested in pericarditislike changes seen in electrocardiography. The sensitivity of the electrocardiogram for myocarditis is low (47%). In some cases, fascicular block or atrioventricular conduction disturbances and ventricular tachyarrhythmia may be hemodynamically significant.
- B. Echocardiogram.** A complete echocardiogram is standard procedure for patients with suspected myocarditis to exclude alternative causes of heart failure, detect the presence of intracardiac thrombi and associated valvular disease, and quantify the degree of left ventricular (LV) dysfunction to monitor response to therapy.
 1. Occasionally, focal wall motion abnormalities and presence of pericardial fluid may prompt further workup or intervention.
 2. Fulminant myocarditis is often characterized by near-normal diastolic dimensions and increased septal wall thickness, whereas acute myocarditis often has increased diastolic dimensions but normal septal wall thickness.
 3. In a series of 23 patients with biopsy-proven myocarditis, significant reduction in right ventricular function was a powerful predictor of death or the need for cardiac transplantation.
- C. Other imaging modalities**
 1. **Antimyosin scintigraphy (indium III monoclonal antimyosin antibody)** provides identification of myocardial inflammation, with a high sensitivity (91% to 100%) and negative predictive value (93% to 100%) but low specificity (28% to 33%).
 2. **Gallium scanning** identifies severe myocardial cellular infiltration with high specificity (98%) but low sensitivity (36%).
 3. **Gadolinium-enhanced magnetic resonance imaging (MRI)** is being used more frequently for diagnosis based on several small observational studies that have found up to 100% sensitivity and specificity depending on the protocol. In one study, MRI was also used for guiding biopsy to areas of focal increased uptake of gadolinium in patients with clinically suspected myocarditis with significantly higher diagnostic yield compared with those who did not have enhancing areas with which to guide the biptome.
- D. Coronary angiography.** Cardiac angiography is often indicated to rule out coronary artery disease as the cause of new-onset heart failure, as the clinical presentation of myocarditis may mimic myocardial infarction (i.e., pseudoinfarct pattern), especially if there are focal wall motion abnormalities and localizing electrocardiographic changes.

V. ETIOLOGY. Up to 50% of all cases may not have a clear underlying cause (i.e., idiopathic cases).

A. Infective causes (Table 11.1)

- 1. Viral myocarditis.** Cardiotropic viruses such as enteroviruses (specifically the coxsackie group B and echoviruses) may cause direct cardiotoxic injuries, cytokine activation, cytoskeletal damage, and autoimmune responses. However, data suggest that the incidence of myocarditis after infection is lower than previously projected. Viral myocarditis is often considered when accompanied with a clinical

TABLE 11.1 Causes of Myocarditis

Cause	Examples
Infectious causes	
Viruses	Enteroviruses, coxsackievirus A and B, echovirus, influenza virus, poliovirus, herpesviruses, adenovirus, mumps, rubella, rubeola, hepatitis B or C virus, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, and parvovirus B19
Rickettsia	Rocky Mountain spotted fever
Fungi	Cryptococcosis, aspergillosis, coccidioidomycosis, and histoplasmosis
Protozoa	<i>Trypanosoma cruzi</i> (Chagas disease) and <i>Toxoplasmosis gondii</i>
Helminths	Trichinosis and schistosomiasis
Bacteria	<i>Legionella</i> , <i>Clostridium</i> , streptococci, staphylococci, <i>Salmonella</i> , and <i>Shigella</i>
Spirochetes	<i>Borrelia burgdorferi</i> (Lyme disease)
Noninfectious causes	
Hypersensitive reaction	Eosinophilic myocarditis
Cardiotoxic drugs	Catecholamines, amphetamines, cocaine, chemotherapeutic drugs (e.g., anthracyclines, fluorouracil, streptomycin, cyclophosphamide, interleukin-2, trastuzumab [Herceptin]), and small pox vaccine
Collagen vascular diseases	Systemic lupus erythematosus (i.e., lupus carditis), Wegener's granulomatosis or Churg-Strauss syndrome, dermatomyositis or polymyositis, and scleroderma
Systemic illnesses	Sarcoidosis, giant cell myocarditis, Kawasaki disease, large-vessel vasculitis (e.g., polyarteritis nodosa and Takayasu arteritis), and inflammatory bowel diseases (e.g., ulcerative colitis and Crohn disease)
Acute rheumatic fever	
Bites and stings	Venoms of scorpions, snakes, wasps, and black widow spiders
Chemicals	Hydrocarbons, carbon monoxide, thallium, lead, arsenic, and cobalt
Physical injury	Irradiation, heatstroke, and hypothermia
Childbirth	Peripartum cardiomyopathy
Alloantigens	Posttransplantation cellular rejection

picture of recent febrile illness, often with prominent myalgias, followed by rapid onset of cardiac symptoms. However, direct proof is lacking (and often unnecessary), and many cases of idiopathic dilated cardiomyopathies have been attributed to antecedent viral myocarditis. Antiviral therapies have not proved to be useful.

2. **Chagas disease.** Cardiomyopathy caused by *Trypanosoma cruzi* in South and Central America, particularly in persons aged 30 to 50 years. It is estimated that 16 to 18 million persons are infected with *T. cruzi* in Latin America. Cardiac involvement usually appears decades after initial treatment and is the leading cause of death of persons aged 30 to 50 years in the endemic areas.

a. Diagnosis

- (1) Serologic test results should be positive for at least two types of tests (i.e., indirect immunofluorescence, indirect hemagglutination, complement fixation, immunoenzymatic, and radioimmune assays).
- (2) Cardiac lesions diagnosed by in situ polymerase chain reaction methods of analyzing biopsies.
- (3) Typical electrocardiographic changes include right bundle branch block with left anterior hemiblock, premature ventricular complexes, T-wave inversions, abnormal Q waves, variable atrioventricular blocks, low QRS voltage, and sick sinus syndrome.
- (4) Echocardiographic findings include LV aneurysm with or without thrombi, posterior basal akinesis or hypokinesis with preserved septal contraction, and diastolic dysfunction.

b. Clinical presentation

- (1) The acute and subacute phases (i.e., 4 to 8 weeks of acute inflammation) consist for the most part of local inflammation at the parasite entry site and flulike symptoms. Occasionally hepatosplenomegaly and lymphadenopathy occur, but concomitant meningoencephalitis is rare. These manifestations often result from pathogen-induced cytotoxicity and inflammatory responses. More than 90% of cases resolve in 4 to 8 weeks without therapy.
- (2) The chronic phase (up to 10 to 30 years after acute infection) manifests with symptoms of palpitations, syncope, chest pain, and, subsequently, heart failure. Approximately 5% to 10% of affected patients may develop direct acute-to-chronic progression.
 - (a) Heart failure (predominantly right sided in advanced stages) may develop in 25% to 30% of those affected.
 - (b) Cerebral or pulmonary thromboembolism may occur in 10% to 15% of those affected.
 - (c) Concomitant megaesophagus or megacolon may develop.
 - (d) Apical LV aneurysm and apical fibrosis may develop.
- (3) Chagas disease is highly arrhythmogenic.
 - (a) Frequent, complex ectopic beats and ventricular tachyarrhythmia occur in 40% to 90% of affected patients, with sudden cardiac death occurring in 55% to 65%.
 - (b) Bundle branch block occurs in 50% of affected patients, and bradyarrhythmia with high-grade atrioventricular block occurs in 7% to 8%.
 - (c) Atrial fibrillation develops in 7% to 10% of affected patients.
- c. Antibiotic therapy aims to reduce parasitemia and prevent complications.
 - (1) Benznidazole (5 to 10 mg/kg/d q12h for 60 days) or
 - (2) Nifurtimox (8 to 10 mg/kg po q24h for 90 to 120 days)
3. **Human immunodeficiency virus (HIV)-related cardiomyopathy.** HIV disease has been recognized as an important cause of dilated cardiomyopathy, with an estimated incidence of 1.6%. HIV type 1 (HIV-1) virions appear to infect myocardial cells in patchy distributions, leading to cytokine activation and progressive tissue damage. Cardiac autoimmunity, nutritional deficiencies, and drug

toxicities (i.e., mitochondrial damage from zidovudine and vasculitis or coronary artery disease associated with highly active antiretroviral therapy regimens) are possible contributing causes. In addition, other known viral pathogens, including cytomegalovirus, Epstein-Barr virus, and coxsackievirus B, have been isolated from endomyocardial biopsy (EMB) specimens of HIV-positive patients with myocarditis in conjunction with HIV nucleic acid sequences, suggesting that opportunistic viral infections may play an important role in the pathogenesis of this type of cardiomyopathy.

B. Peripartum cardiomyopathy (see Chapter 38)

C. Giant cell myocarditis (see Chapter 38), pernicious myocarditis, Fiedler's myocarditis, granulomatous myocarditis, or idiopathic interstitial myocarditis): This is a rare disorder with an unclear origin. The **hallmark feature is the presence of fused, multinucleated (> 20 nuclei) epithelioid giant cells of histiocytic origin within a diffuse, intramyocardial inflammatory infiltrate with lymphocytes.**

1. GCM often presents with an **aggressive clinical course**, with progression over days to weeks. Rapidly progressive heart failure is the presentation in 75% of affected patients. Sustained ventricular tachyarrhythmia occurs in 29% of patients with GCM and atrioventricular block occurs in 50%.
2. The prognosis is **dismal without therapy**, but the disease is often refractory to standard medical therapy, with a 1-year mortality rate of up to 80% (median survival of 3 to 5 months from symptom onset).
3. Small observational series have suggested potential benefits of immunosuppressive therapy, and a randomized, prospective multicenter study is ongoing. Consideration for **early cardiac transplantation** is appropriate (71% 5-year survival after successful transplantation). Often, mechanical support may be required as a temporary bridge to recovery or transplantation. A 20% to 25% rate of histologic recurrence in surveillance EMBs has been observed after transplantation.

D. Hypersensitive reaction (i.e., eosinophilic myocarditis). Eosinophilic endomyocardial disease (i.e., Loeffler's endomyocardial fibrosis, see Chapter 9) occurs as a major complication of idiopathic hypereosinophilic syndrome as a result of direct toxic damage caused by eosinophil granule proteins within the heart. Drug-induced eosinophilic myocarditis is independent of cumulative dose and duration of therapy.

The absence of peripheral eosinophilia does not rule out eosinophilic myocarditis. Although observational series suggest potential clinical benefits of corticosteroid therapy, the best strategy is to remove the causative agent when known.

1. Medications that may cause eosinophilic myocarditis include the following:
 - a. Antibiotics (e.g., ampicillin, chloramphenicol, tetracycline, and sulfisoxazole)
 - b. Diuretics (e.g., hydrochlorothiazide and spironolactone)
 - c. Anticonvulsants (e.g., phenytoin and carbamazepine)
 - d. Other drugs (e.g., lithium, clozapine, and indomethacin)
 - e. Tetanus toxoid
 2. Collagen vascular diseases such as Wegener's granulomatosis or Churg-Strauss syndrome (i.e., allergic granulomatosis and vasculitis) may also lead to eosinophilic myocarditis.
 3. Other causes include parasitic infection, drug hypersensitivity, and cellular rejection after cardiac transplantation, as well as postvaccinia myocarditis after small pox vaccination.
- E. Systemic autoimmune disorders with myocarditis.** Although the histologic appearance of myocarditis occurring as part of sarcoidosis, systemic lupus erythematosus, or polymyositis is similar to that seen in isolated myocarditis, the natural history is different. **Systemic causes of myocarditis often respond poorly to medical therapy and cardiac transplantation**, and their prognoses are often unfavorable. However, small retrospective surveys and case series have identified a significant decrease in mortality and improved clinical course among cardiac sarcoid patients treated with corticosteroids and other immunosuppression strategies.

VI. PROGNOSIS. On the basis of population studies, adults with myocarditis may present with few symptoms or with an acute toxic state of cardiogenic shock or frank heart failure (i.e., fulminant myocarditis). However, adults may present with heart failure years after the initial index event of myocarditis (up to 12.8% of patients with idiopathic dilated cardiomyopathy had presumed prior myocarditis in one case series).

A. Natural history and sequelae of myocarditis. The outlook is poor in the acute phase, regardless of clinicopathologic classification, but those surviving the acute phase have a more favorable prognosis (except for those with chronic active myocarditis).

1. Many patients may have **full spontaneous clinical recovery**, even after weeks of mechanical support (e.g., intra-aortic balloon counterpulsation and mechanical assist devices).
2. In the Myocarditis Treatment Trial, the 1-year mortality rate was 20% and the 4-year mortality rate was 56%.
3. In-hospital case series point to an 11-year survival rate of 93% for patients with fulminant myocarditis and 45% for nonfulminant myocarditis.
4. Evolution to dilated cardiomyopathy
 - a. Up to one-half of patients with myocarditis develop subsequent cardiomyopathy over a range of 3 months to 13 years.
 - b. Histologic evidence of myocarditis is seen in 4% to 10% of EMBs of patients with idiopathic dilated cardiomyopathy.
5. Severe heart block requiring permanent pacemaker placement occurs in 1% of patients.

B. Predictors for morbidity and mortality

1. Unfavorable factors for survival include extremes of **age** (i.e., very old or very young), **electrocardiographic abnormalities** (e.g., QRS alterations, atrial fibrillation, and low voltages), **syncope**, and **specific diagnoses** (e.g., peripartum cardiomyopathy and GCM).
2. Favorable factors for survival include normal ventricular function, shorter clinical history, and fulminant presentation at onset.

VII. TREATMENT

A. Heart failure management

1. Patients who present with myocarditis with acute dilated cardiomyopathy should be treated according to the current American Heart Association, the American College of Cardiology, the European Society of Cardiology, and the Heart Failure Society of America (HFSA) guidelines. Standard heart failure therapy consists of diuretics, angiotensin-converting enzyme inhibitors, β -blockers, and aldosterone antagonists. Studies have not been done to determine when and how to discontinue standard heart failure therapy in patients who recover LV function.
2. Because of its proarrhythmic properties in animal models, digoxin should be avoided.
3. Anticoagulation to prevent thromboembolic events is usually recommended in patients with apical aneurysm with thrombus (e.g., Chagas disease, atrial fibrillation, and prior embolic episodes).
4. Inotropic therapy is reserved for severe hemodynamic compromise, particularly in fulminant myocarditis.
5. Aggressive support with mechanical and surgical intervention is often indicated (see Chapters 8 and 12).
 - a. Intra-aortic balloon counterpulsation for hemodynamic support and after-load reduction
 - b. Mechanical assistive devices (left ventricular assist device)
 - c. Extracorporeal membrane oxygenation

6. Early consideration for cardiac transplantation should be given, especially for patients with progressive, biopsy-proven GCM or peripartum cardiomyopathy. However, patients with myocarditis have increased rates of rejection and reduced survival after heart transplantation compared with those without myocarditis, and recurrent disease may affect the allograft.
- B. Exercise restriction**
1. There is a theoretical increased risk of myocardial inflammation and necrosis, cardiac remodeling, and death, as shown in animal models.
 2. Patients are usually advised to abstain from vigorous exercise for up to 6 months or longer after the onset of symptoms. The length of activity restriction can be based on recovery of LV function.
- C. Arrhythmia management**
1. Antiarrhythmics provide the first-line treatment using standard therapy such as β -blockers, amiodarone, and sotalol.
 2. Implantable cardioverter–defibrillators are used for patients stabilized in the chronic phase with persistently low ejection fraction (EF) and for those with malignant arrhythmias that are refractory to medical therapy.
 3. Permanent pacemakers are used for heart block or bradyarrhythmia.
- D. Follow-up**
1. Clinical follow-up should be close because persistent chronic inflammation may lead to dilated cardiomyopathy. Initially, 1- to 3-month intervals are used for drug and physical activity titration.
 2. Serial echocardiographic assessment of ventricular structure and function is often performed, although there is no agreement regarding the frequency of echocardiographic assessment after myocarditis.
- E. Immunosuppressive therapy is reserved for refractory disease or biopsy-proven GCM.** No benefits have been established for antiviral regimens or nonsteroidal antiinflammatory agents (see Section **VIII.B**). The most recent HFSA guidelines do not recommend routine use of immunosuppressive therapy in patients with myocarditis. More work is needed to identify patient cohorts who will benefit from tailored antiviral and immunosuppressive therapy.

VIII. CONTROVERSIES IN MYOCARDITIS

A. Endomyocardial biopsy

1. **Routine EMB confirmation of myocarditis is unnecessary.**
 - a. EMB can be considered in those patients with a **rapid deterioration in cardiac function** of unknown etiology who do not respond to standard medical therapy.
 - b. Incidence of biopsy-proven myocarditis in recent-onset, unexplained heart failure can be as low as 8% to 10%. Concerns have emerged that this is caused by low sensitivity of the Dallas criteria, and several recent trials of immunosuppressive therapy have utilized supplemental pathologic criteria to assess myocarditis, including upregulation of human leukocyte antigen, presence of virus, and antiscardiac antibodies.
 - c. **False-negative rates are high** (50% even in four or five biopsies) because of the small number of lymphocytes and difficulties in distinguishing cell types, with wide interobserver variability.
2. However, EMB may be considered in patients with the following conditions in which a diagnostic biopsy may provide information on prognosis and/or therapeutic possibilities (see Table 11.2):
 - a. Rapidly progressive heart failure symptoms despite conventional therapy or new-onset frequent ventricular tachyarrhythmia or conduction disturbances
 - b. Suspected specific causes of myocarditis (e.g., GCM, eosinophilic myocarditis, cardiac sarcoidosis, and vaccinia myocarditis)

TABLE 11.2 Relevant ACC/AHA Recommendations for the Role of Endomyocardial Biopsy

Scenario	Class of recommendation
New-onset heart failure of < 2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	I
Heart failure of > 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	IIa
Heart failure associated with a dilated cardiomyopathy of any duration associated with suspected allergic reaction and/or eosinophilia	IIa
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, or second- or third-degree heart block that responds to usual care within 1–2 weeks	IIb
Heart failure of > 3 mo duration associated with a dilated left ventricle, without new ventricular arrhythmias, or second- or third-degree heart block that responds to usual care within 1–2 wk	IIb
Unexplained ventricular arrhythmias	IIb

Adapted from Cooper LT, Baughman KL, Feldman AM, et al. The role of endomyocardial biopsy in the management of cardiovascular disease. *Circulation* 2007; 116: 2216–2233.

3. Although specificity is high (98%), sensitivity has been found in some series to be as low as 10% to 22%. It increases with multiple biopsies, but postmortem examinations have found that more than 17 specimens were needed to make the diagnosis with 80% sensitivity in proven myocarditis cases.
4. **Biopsy** for staging of myocarditis:
 - a. Cell types include lymphocytic, eosinophilic, neutrophilic, giant cell, granulomatous, and mixed.
 - b. Amount of cells: none (grade 0), mild (grade 1), moderate (grade 2), and severe (grade 3).
 - c. Distribution: focal (i.e., outside of vessel lumen), confluent, diffuse, and reparative (i.e., in fibrotic areas).
5. Other tests:
 - a. Immunohistochemical staining to examine upregulation of major histocompatibility complex antigens and quantify inflammation, although rates of correlation with biopsy-proven myocarditis have not been consistent between studies.
 - b. Approximately 12% to 50% of patients with acute or chronic myocarditis have persistent viral mRNA detected in biopsy samples.
- B. **Immunosuppressive therapy** in acute myocarditis
 1. Routine immunosuppressive therapy is not recommended because of the neutral findings from multiple trials, including the Myocarditis Treatment Trial and the Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study. There is no Food and Drug Administration (FDA)–approved regimen for the treatment of acute or chronic myocarditis.

2. Considerations are reserved for patients with new-onset, rapidly deteriorating, advanced heart failure with suspicion of the following conditions:
 - a. GCM is treated with combination therapy (Table 11.3).
 - b. Eosinophilic or sarcoid myocarditis is treated with high-dose steroids.
 - c. Specific therapy is used for underlying collagen vascular diseases, if present.

TABLE 11.3 Treatment Regimens for Myocarditis in Clinical Trials

Intervention in Myocarditis and Acute Cardiomyopathy (IMAC) study^a

Intravenous immune globulin (Gamimune N, 10%): 1 g/kg/d IV \times 2 d

Giant Cell Myocarditis study^b

Cyclosporine: 25 mg po bid, increase by 25 mg increments to target level:

Monoclonal whole-blood immunoassay: 200–300 ng/mL

High-performance liquid chromatography assay: 150–250 ng/mL

Fluorescence polarization immunoassay serum-based polyclonal assay: 100–150 ng/mL

Dose reduction if renal dysfunction develops

Muromonab-CD3 (OKT-3): 5 mg IV qd \times 10 d

Dose reduction if hypotension develops

Corticosteroid: methylprednisolone, 10 mg/kg IV qd \times 3 d, followed by prednisone, 1–1.25 mg/kg with extended taper

Azathioprine: 200 mg po qd

Myocarditis Treatment Trial^c

Corticosteroid/cyclosporine versus corticosteroid/azathioprine versus placebo (biopsy-proven myocarditis, LVEF < 45%, NYHA \geq class II)

Oral prednisone: 1.25 mg/kg/d in divided doses \times 1 wk; reduce oral dose by 0.08 mg/kg/wk until dose is 0.33 mg/kg/d at week 12; maintain oral dose until week 20 and then reduce dose by 0.08 mg/kg/wk until week 24; then off.

Oral cyclosporine: 5 mg/kg bid to achieve level of 200–300 ng/mL \times 1 wk; adjust oral dose to achieve level of 100–200 ng/mL from weeks 2 to 4; adjust oral dose to achieve level of 60–150 ng/mL from weeks 4 to 24.

Immunosuppressive therapy for active lymphocytic myocarditis^d

Prednisone 1 mg/kg/d for 4 wk; reduced to 0.33 mg/kg/d for 5 mo; azathioprine 2 mg/kg/d for 6 mo

LVEF, Left ventricular ejection fraction; NYHA, New York Heart Association.

^aMcNamara DM, Holubkov R, Starling RC, et al. Controlled trial of intravenous immune globulin in recent-onset dilated cardiomyopathy. *Circulation*. 2001;103:2254–2259.

^bRosenstein ED, Zucker MJ, Kramer N. Giant cell myocarditis: most fatal of autoimmune diseases. *Semin Arthritis Rheum*. 2000;30:1–16.

^cMason JW, O'Connell JB, Herskowitz A, et al. A clinical trial of immunosuppressive therapy for myocarditis. The Myocarditis Treatment Trial Investigators. *N Engl J Med*. 1995;333:269–275.

^dFrustaci A, Chimenti C, Calabrese F, et al. Immunosuppressive therapy for active lymphocytic myocarditis: virological and immunologic profile of responders versus nonresponders. *Circulation*. 2003;107:857–863.

3. Studies are ongoing in an attempt to identify markers to predict favorable response to immunosuppressive regimens. A study of 112 patients with histopathologic acute lymphocytic myocarditis who failed to improve with conventional therapy and subsequently received prednisone and azathioprine found that one-half of the treated group improved, with EF rising from 26% to 47% and improvement in biopsy findings. Of those who failed conventional therapy, those patients who responded to immunosuppression were significantly more likely to have positive cardiac antibodies (90% vs. 0%) and less likely to have viral persistence when compared with nonresponders (14% vs. 85%).

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Nontransplantation Surgical Treatment for Chronic Heart Failure

I. INTRODUCTION. Even with optimal medical therapy, the morbidity and mortality associated with chronic heart failure (CHF) is significant. Fortunately, there are multiple possible surgical interventions available for these patients that may help to avoid or postpone the need for advanced salvage therapies and transplantation. Despite the improvement in surgical techniques and an enhanced understanding of the role of reconstructing structural abnormalities of the failing heart, safety and efficacy data are still limited for many of these procedures. Elective and planned procedures for advanced heart failure (e.g., revascularization, valvular surgery, left ventricular [LV] reconstructive surgery, and cardiomyoplasty) and urgent or bridging procedures (e.g., circulatory support devices and total artificial heart [TAH]) are discussed in this chapter. Surgical approaches to the management of heart failure must be accompanied by continued aggressive pharmacologic therapy.

II. SURGICAL REVASCLARIZATION FOR ISCHEMIC CARDIOMYOPATHY

A. Pathophysiology

1. Loss of coronary flow reserve in severe coronary artery disease leads to reduction in myocardial perfusion, tissue hypoxia, and myocardial dysfunction.
2. Myocardial infarction results in necrosis, scarring, and loss of contractile function. Sites distal to infarction undergo increased mechanical stress and adverse remodeling over time. Progressive ventricular dilation and impairment of systolic and diastolic function occur.
3. Chronic ischemia can decrease perfusion, leading to hibernation, repeated episodes of stunning, and recurrent infarction. The cardiomyocytes may shift metabolic states to hibernation. Thus, revascularization may help retain viability and recover function. Stunning and hibernation may be detected by various imaging modalities (see Chapter 50).
 - a. **Stunning** is the loss of contractile function caused by a momentary total occlusion of blood flow with subsequent restoration of flow.
 - b. **Hibernation** is the downregulation of myocardial function to match the chronic reduced blood flow. Hibernating cardiomyocytes manifest sustained glucose extraction, decreased glycogen content, and decreased contractile proteins and function.

B. Clinical significance

1. Heart failure, rather than angina or an acute coronary syndrome, is a common presentation of myocardial ischemia in patients with underlying cardiac dysfunction.
2. At least two-thirds of patients with cardiac dysfunction have evidence of epicardial coronary artery disease as the primary etiology. Coronary angiography is indicated when the suspicion of an ischemic cause for cardiomyopathy is high.

3. Some patients may have epicardial coronary artery disease superimposed on an underlying dilated cardiomyopathy. In this scenario, the presence of epicardial coronary artery disease may not necessarily explain the “degree” of depressed myocardial contractility. The role of revascularization remains unclear for these patients.

C. Recommendations

1. Most recently, the Surgical Treatment for Ischemic Heart Failure (STICH) trial reported that in patients with coronary artery disease amenable to coronary artery bypass grafting (CABG) and left ventricular ejection fraction (LVEF) < 35%, there was no difference in the trial’s primary end point of all-cause mortality when treated with optimal medical therapy versus CABG. However, benefit was seen in the CABG group with respect to the secondary end point of cardiovascular death at follow-up. There were several limitations to this study: 30-day mortality was high in the CABG group and significant crossover occurred, both of which may have diminished the benefits of CABG in the primary intention to treat analysis.
2. Primary CABG should still be considered for patients with an LVEF > 15%, LV end-diastolic dimensions < 65 mm, distal vessels suitable for grafting, and evidence of a significant amount of ischemic or hibernating myocardium. These guidelines are arbitrary and many centers consider patients with more severe diseases.
3. Patients with hibernating myocardium and severe LV dysfunction who undergo CABG may achieve survival advantage comparable to those receiving cardiac transplantation (about 80% survival in 3 years).
 - a. The potential for significant improvement in LV function and symptoms is assumed to be great enough to recommend revascularization when there are four or more viable segments of myocardium, representing approximately 31% of the left ventricle.
 - b. Surgical revascularization of the patient with severe heart failure should generally be considered as part of a multifaceted approach, including evaluation for valve repair, ventricular reconstructive surgery, cryoablation for ventricular arrhythmias, and maze procedure or pulmonary vein isolation procedures for atrial dysrhythmias. To maximize the therapeutic benefit from this approach, aggressive complementary pharmacologic approaches are indicated postoperatively.

III. MITRAL VALVE SURGERY

A. Pathophysiology

1. As the ventricle fails, progressive dilation leads to abnormal geometry of the left ventricle, giving rise to mitral regurgitation (MR). MR results in progressive increase in volume overload of the left ventricle, progressive LV dilation, and further worsening of MR.
2. Other alterations of the annular–ventricular apparatus and ventricular geometry contribute to the pathogenesis of MR: papillary muscle ischemia or infarction, myocardial thinning and dilation, blunting of the aortomitral angle, widening of the interpapillary distance, and increased leaflet tethering leading to loss of the zone of coaptation.

B. Clinical significance and recommendations

1. Restoration of zone of coaptation by inserting an “undersized” annuloplasty ring may correct the MR and improve the LV geometry and cardiac output. However, mitral valve repair in ischemic cardiomyopathy (“ischemic MR”) is less successful than in degenerative MR.
2. Subvalvular apparatus should be kept intact when possible.

3. In some patients, mitral valve surgery results in improved symptoms and measures of LV function and remodeling but not necessarily in improved survival.
4. In some patients, mitral valve repair with a figure-of-eight stitch (i.e., Alfieri approach) or the “edge-to-edge” technique may be used in addition to annuloplasty to secure the repair.
5. Mitral valve replacement is required in a minority of patients and may be associated with a significantly worse outcome.

IV. LV RECONSTRUCTIVE PROCEDURES

A. Pathophysiology

1. Laplace's law dictates that as the failing heart dilates, the intracavity radius increases and thus wall stress increases. The result is increased myocardial oxygen consumption and stimulation of adverse remodeling.
2. Surgical remodeling helps to decrease ventricular size and wall stress. Endoventricular circular patch plasty (EVCPP, also called the Dor procedure) is performed in patients with ischemic cardiomyopathy and significant areas of LV akinesis or dyskinesis. Partial LV resection, also called the Batista procedure, was performed in the past on patients with dilated, nonischemic cardiomyopathy. This was abandoned because of poor intermediate results and increased mortality, despite promising short-term outcomes.

B. Endoventricular circular patch plasty

1. Acute myocardial infarction leads to tissue necrosis, scar formation, followed by LV remodeling, leading to dilation and heart failure. The Dor procedure is suitable for patients with a left anterior descending artery territory scar or aneurysm with relatively preserved lateral and posterior LV wall function.
 - a. It involves opening of the akinetic or dyskinetic scar and placement of a purse-string suture at the neck of the aneurysm. The residual opening may be closed with a Dacron patch, after which the ventriculotomy is closed by running sutures.
 - b. This procedure is accompanied by CABG in >90% of cases. Additional valve and ablative surgical procedures are commonly performed.
 2. Good candidates for EVCPP include patients with LV aneurysm (or large akinetic area), an increased LV end-systolic index, absence of scar in the circumflex territory, as well as good target tissue and viability for concomitant CABG. Assessment of the severity of MR is needed at the time of surgery, and mitral valve repair is performed in 30% to 50% of patients undergoing EVCPP.
 3. EVCPP results in improved LVEF, end-diastolic and end-systolic volume indices for LV volumes, and improvement in New York Heart Association (NYHA) functional class.
 - a. In a series of patients with advanced heart failure, the event-free survival rate was 98% at 1 year, 95.8% at 2 years, and 82.1% at 5 years.
 - b. Independent predictors of mortality include higher preoperative NYHA class, lower LVEF (< 30%), higher end-systolic volume index, and remote asynergy.
 - c. Interestingly, the STICH trial demonstrated that despite the reduced LV volume, there was no difference in symptoms, exercise tolerance, hospitalization, and death in patients who received CABG with surgical ventricular reconstruction versus CABG alone. On the basis of this trial, surgical ventricular reconstruction may not add any benefit to HF patients with documented ischemia who are on optimal medical management.
- C. Partial LV resection (i.e., **Batista procedure**) involves the resection of myocardium at the posterolateral wall between the anterolateral and the posteromedial papillary

muscles in nonischemic cardiomyopathy, with or without mitral annuloplasty or mitral valve replacement. For the reasons previously stated, this procedure is no longer performed.

D. Dynamic cardiomyoplasty

1. The procedure involves the mobilization of the entire latissimus dorsi muscle to be used as a pedicle graft. The muscle is passed into the thoracic cavity through a window created by removing the left second rib. The muscle is wrapped around the heart and anchored posteriorly, adjacent to the right atrium and pulmonary artery, and anteriorly around the right ventricle.
 - a. Sensing electrodes are placed epicardially on the right ventricle, and intramuscular stimulator electrodes are placed in the latissimus muscle.
 - b. The muscle conditioning process takes place 2 weeks after surgery and involves the delivery of a single pulse with every other cardiac cycle for 2 weeks. The signal is then incrementally increased every 1 to 2 weeks for 12 weeks.
2. Cardiomyoplasty is believed to work by systolic augmentation of the failing left ventricle and the girdling effect of the muscle acting as an elastic constraint. This prevents LV dilation and improves symptoms, but has no proven survival advantages. Indeed, early mortality is high, especially in those with NYHA class IV status. This procedure is rarely performed now, and data are lacking on its long-term efficacy.
3. Approximately 80% to 85% of surviving patients show NYHA class improvement (mean 1.4 classes). A phase II multicenter FDA study demonstrated significant improvement in LVEF, LV stroke work, and stroke index.
4. Mortality of surgery for class III patients has been < 10%.
5. Hypertrophic obstructive cardiomyopathy is considered to be a relative contraindication.

V. CIRCULATORY SUPPORT DEVICES (I.E., MECHANICAL ASSIST DEVICES)

A. Background

1. Mechanical circulatory assistance is necessary for patients with hemodynamic compromise that are unlikely to survive without a transplant or advanced salvage therapies. Mechanical circulatory support devices may help bridge the patients to recovery or transplantation.
2. The types of devices include the following: intra-aortic balloon counterpulsation pump (IABP), extracorporeal membrane oxygenation (ECMO), univentricular and biventricular nonpulsatile and pulsatile ventricular assist devices (VADs), and the TAH.
3. The decision about which device to use is based on the predicted duration of use, the reversibility of the underlying condition that caused cardiogenic shock, need for single-chamber versus dual-chamber support, and the patient's size.

B. Patient selection

1. Mechanical support is generally indicated in patients who have an inability to maintain hemodynamic stability despite maximal pharmacologic support and who usually must meet criteria as candidates for cardiac transplantation:
 - a. Systolic blood pressure < 75 to 80 mm Hg
 - b. Cardiac index of < 1.5 to 1.8 L/min/m²
 - c. Pulmonary venous saturation < 50%
2. Indications for short-term circulatory support devices include the following:
 - a. Cardiogenic shock after cardiac surgery
 - b. Acute myocardial infarction with cardiogenic shock
 - c. Acute (fulminant) myocarditis
 - d. Cardiac arrest as a complication of interventional cardiac procedures (associated with high mortality and poor survival rates)

3. The 2006 International Society for Heart and Lung Transplantation (ISHLT) guidelines for cardiac transplant candidates:
 - a. The most recent ISHLT recommendations give a class I recommendation to thoroughly evaluate other clinical risk factors prior to device implantation. For instance, an inverse relationship between outcome and age > 60 to 65 years has been reported. However, age by itself should not be a contraindication to implantation.
 - b. Patients with serum creatinine > 3.0 mg/dL are at higher risk but may be considered candidates for implantation if renal failure is acute and recovery is likely (class I).
 - c. Pulsatile intracorporeal devices should only be implanted in patients with body surface area (BSA) > 1.5 m².
 - d. In patients with abnormal liver function tests secondary to right ventricular (RV) failure, biventricular support should be considered. In addition, biventricular support should be considered in those with irreversible pulmonary hypertension, RV failure, or multiorgan dysfunction.
 - e. Active infection should be identified and treated before implantation.
4. If recovery is anticipated, the best option is to use the least traumatic, least complicated device for the individual patient. If recovery of ventricular function is not expected, patients should be considered for the use of a long-term implantable device.

C. Short-term devices

1. Intra-aortic balloon counterpulsation pump

- a. IABP should be placed percutaneously under fluoroscopy so that the tip is about 2 cm below the left subclavian. Height of the patient will determine the size of the IABP (40 cc balloon for the average-sized male). Swan-Ganz catheter and arterial line are encouraged and typically required for hemodynamic monitoring.
- b. IABP enhances coronary blood flow during inflation and decreases oxygen demand by reducing systolic pressure and LV wall stress during deflation. As a result, myocardial consumption and cardiac work are decreased while cardiac output is increased.
- c. Indications: Cardiogenic shock, severe mitral stenosis, decompensated critical aortic stenosis, ventricular septal defect/rupture, refractory ischemia, ischemia ventricular tachycardia, and bridge to definitive therapy.
- d. Contraindications: Hemodynamically significant aortic insufficiency (≥3+), abdominal or thoracic aortic aneurysm/dissections, severe coagulopathy, and sepsis.

2. Extracorporeal membrane oxygenation

- a. ECMO is an extracorporeal system that uses a centrifugal pump to drive blood from the patient to a membrane oxygenator system for carbon dioxide and oxygen exchange.
- b. The femoral artery and vein are cannulated for peripheral access, but the aorta and right atrium can be used as well. The blood is driven from the venous system to the pump and oxygenator and then back into the arterial system.
- c. The device requires systemic anticoagulation and may cause substantial trauma to blood components.
- d. ECMO has the advantage of providing oxygenation in the presence of severe pulmonary dysfunction resulting in hypoxemia. It can also unload both the right ventricle and left ventricle.
- e. The large number of possible complications makes ECMO suitable only for short-term use. It is generally used as a bridge to transplantation, VAD implantation, or other types of definitive therapy.

3. **Percutaneous LV support devices** (TandemHeart, Reitan Catheter Pump, and Impella Recover) are indicated only for short-term use (up to 5 days) and are similar to an IABP with respect to decreasing afterload and myocardial oxygen consumption. Unlike an IABP, these devices completely unload the ventricle rather than simply augmenting it.
 - a. The Impella (LP2.5 and LP5.0) is a catheter-based system inserted through the femoral artery that provides hemodynamic support by an axial pump. Blood is pumped directly from the left ventricle to the ascending aorta.
 - b. The Impella LP2.5 and LP5.0 can provide cardiac output support of up to 2.5 and 4.5 L/min, respectively, depending on the maximum speed of the rotor.
 - c. The TandemHeart system is an extracorporeal continuous-flow centrifugal assist device that provides hemodynamic support via a left atrial-to-femoral bypass with up to a maximum cardiac output of 5.0 L/min. Oxygenated blood is withdrawn from the left atrium via a transseptal cannula and pumped into the femoral artery.
 - d. Both systems require anticoagulation with heparin, prolonged supervision, and bed rest.
 - e. Hemodynamic support from the Impella and TandemHeart can be continued for up to 5 days.
 - f. These devices can potentially be used to support patients with acute MI with cardiogenic shock, patients with decompensated heart failure with myocarditis, and during high-risk percutaneous coronary intervention or valvuloplasty. The TandemHeart can be used for RV support if the catheters are placed so as to pump from the right atrium to the pulmonary artery.
 - g. Recent trials for the Impella 2.5, namely, PROTECT I, ISAR-SHOCK (vs. IABP), AMC-MACH2 (vs. IABP), PROTECT II (vs. IABP), RECOVER II (vs. IABP), and EUROPELLA, demonstrated more favorable hemodynamics, reduction in infarct size, as well as reduction in 30-day major adverse cardiac event.
 - h. There is a paucity of data regarding clinical outcomes and safety of patients with TandemHeart despite this being commercially available since 2004.
 - i. See Table 12.1 for contraindications and potential adverse events.

TABLE 12.1**Contraindications to and Cautions with Percutaneous Left Ventricular Support Devices**

Devices	Contraindications	Potential adverse events
Impella	Mural thrombus in the left ventricle, mechanical aortic valve, constrictive heart device, severe peripheral arterial disease, moderate to severe aortic stenosis ($\geq 2+$) and regurgitation ($\geq 2+$), severe aortic tortuosity, and calcification	Aortic regurgitation, aortic valve injury, arrhythmias, bleeding, tamponade, infection, stroke/transient ischemic attack, hemolysis, limb ischemia
TandemHeart	Moderate to severe aortic stenosis ($\geq 2+$) and regurgitation ($\geq 2+$), severe peripheral vascular disease	Bleeding, a femoral arteriovenous fistula, thromboembolic events, atrial septal defect, limb ischemia, wound infection, lymphocele, hypothermia

4. **Centrifugal pumps** such as the BioMedicus Biopump are extracorporeal and are commonly used for biventricular support for small patients ($BSA \leq 1.5 \text{ m}^2$) and also with ECMO.
 - a. The nonpulsatile pump uses a spinning chamber to generate blood flow through rotating cones or by an impeller mechanism.
 - b. The cannulation site for inflow into the pump is the femoral vein, right atrium, or ventricle, and the outflow cannula is placed in the femoral artery, axillary artery, or aorta. The lines are typically left between an unclosed sternum with only skin closure. This necessitates continuous supervision by trained staff and limits the devices to short-term use only.
 - c. Heparin anticoagulation is needed.
5. **Pulsatile pumps** are extracorporeal, asynchronous pumps (e.g., Abiomed BVS5000) that are commonly used for right, left, or biventricular support.
 - a. There are atrial and arterial cannulas. The atrial cannula is put into the right or left atrium, and the arterial cannula is in the aorta. The advantage over centrifugal systems is that subcostal lines allow sternal closure.
 - b. The pump has an upper chamber and a lower chamber. The upper chamber is filled passively by continuous blood flow from the atrium. The lower chamber has two trileaflet polyurethane valves (i.e., inflow and outflow valves) and is designed to eject a stroke volume of approximately 80 mL.
 - c. The pump is pneumatically driven by compressed room air and provides 4 to 5 L/min of pulsatile flow.
 - d. Anticoagulation is recommended with heparin or warfarin sodium to lower the rate of thromboembolism.
 - e. The disadvantages of this system are the lack of mobility and the lower flow rates achieved compared with the chronically implanted devices. A decision is made after 5 to 7 days of support, and if further mechanical support is needed, the Abiomed is removed and a chronic device is implanted.
 - f. In small retrospective studies, outcomes in terms of successful bridge to transplantation, pre- and posttransplant mortality, and hospital discharge have not been shown to be significantly different between pulsatile and nonpulsatile devices.
6. **Axial flow pumps**
 - a. Nonpulsatile rotary pumps are similar to centrifugal flow devices, but these generate the energy for acceleration of blood by deflecting the flow in the circumferential direction using impellers.
 - b. They are smaller and less noisy than other devices, making them a good option for patients with a smaller BSA, as well as potentially decreasing the risk of infection due to smaller pocket size.
 - c. Major complications include an increased tendency for pump thrombus, thus mandating anticoagulation and hemolysis.

D. Longer term implantable devices

1. Pulsatile implantable devices: Thoratec paracorporeal system, the CardioWest TAH, Novacor, and HeartMate XVE are currently used.
 - a. Thoratec is a paracorporeal system that can be used for left, right, or biventricular support. Because the system is outside the body, it can be used in patients with $BSA \leq 1.5 \text{ m}^2$. However, this does limit mobility and flow rates (maximum stroke volume is 65 mL and flow rates can reach 7.2 L/min). Systemic anticoagulation is required.
 - b. The CardioWest TAH is implanted after removal of the native heart and provides complete support. To accommodate the sizable device, patients must have a $BSA > 1.7 \text{ m}^2$ and anteroposterior distance of the chest of $> 10 \text{ cm}$. Systemic anticoagulation is required. This device has been approved for use as a bridge to transplantation. Another TAH, the Abiomed, is in the

investigational stages of development. This device is smaller and provides more mobility.

- c. The Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial randomized patients with end-stage heart failure who required inotropic therapy but were ineligible for cardiac transplantation to a vented electric LVAD or optimal medical therapy. There was a 48% relative reduction in risk of death from any cause in the group that received LVAD compared with the medically treated group. The probability of device failure was 35% at 24 months, and 10 patients had the device replaced. The LVAD group had significant improvement in the quality of life over the trial, but the survival rates with permanent VAD are still far inferior to those for cardiac transplantation. This trial led to the approval of the HeartMate LVAD as a destination therapy in selected patients not eligible for transplant. The follow-up of outcomes in 42 patients who were implanted with destination therapy HeartMate LVAD since the REMATCH trial reveals improved survival rates at 1 month and 1 year and decreased rates of infection and adverse events compared with those found in the trial patients. Occasionally, patients who are implanted with the intent of destination therapy have improvement in conditions such as renal impairment or pulmonary hypertension that had precluded them from eligibility for transplantation earlier in their course and thus are suitable to be reevaluated for transplantation.
2. Axial flow pumps: Jarvik 2000, HeartMate II, and the MicroMed DeBakey.
 - a. Produce continuous nonpulsatile blood flow using a small pump with rotor blades. Bearings of the rotor are in direct contact with the blood.
 - b. MicroMed and HeartMate II have inflow cannulas that insert in the LV apex. The MicroMed and HeartMate II require a sternotomy and are implanted into a small abdominal pocket. The outflow cannula is attached to the descending aorta.
 - c. Jarvik is intraventricular, which eliminates the need for an inlet cannula and eliminates inlet graft kinking, thrombosis, pannus formation in the inlet graft, and inlet obstruction by the septum or lateral wall of the heart. The outflow cannula is attached to the descending aorta. The small size allows the Jarvik to be surgically implanted through a left thoracotomy, with or without cardiopulmonary bypass, and it can be implanted in smaller adults or children.
 - d. Axial flow pump is a true LVAD because it augments LV function. Optimal pump speeds are between 8,000 and 12,000 rpm. Native left ventricle is allowed to eject through the aortic valve, giving some pulsatility to the blood flow.
 - e. Axial flow pumps can generate flows up to 5 to 7 L/min.
 - f. Major complications are thromboembolic events due to inadequate blood flow in the ascending aorta giving rise to thrombus formation and the potential for embolic stroke.
 - g. HeartMate II is the best studied LVAD and in turn has become the standard of care in VADs. Miller and colleagues demonstrated the safety and efficacy of the HeartMate II device when used as a bridge to transplantation. Further studies have demonstrated improved quality of life, functional status, and incidence of end-organ failure. Slaughter and colleagues reported a significant improvement in the quality of life and survival free from stroke and device failure with implantation of a continuous-flow LVAD when compared with a pulsatile-flow device for destination therapy.
 - h. Data describing experience with the Jarvik 2000 showed that the cardiac index increased by 43%, capillary wedge pressure decreased by 52%, and

80% of the patients improved from NYHA class IV to I. No device thrombosis was reported.

E. Contraindications to VADs

1. Uncontrolled sepsis.
2. Aortic valve incompetence needs to be corrected before implantation of the VAD because it might lead to regurgitation of blood from the outflow cannula back into the left ventricle. Severe mitral stenosis should also be treated to avoid limiting the device output due to decreased native ventricular filling.
3. Preexisting mechanical prosthetic valves may need to be changed to bioprosthetic valves to obviate the need for anticoagulation before implanting the VAD.
4. Hypercoagulable states may preclude the placement of VADs not requiring anticoagulation.
5. Aortic aneurysm or dissection may affect the optimal placement of the outflow cannula in the ascending aorta.
6. Bleeding diathesis.
7. Patent foramen ovale or atrial septal defects need to be closed before implantation of VADs to prevent right to left shunting of blood and paradoxical emboli as the left side of the heart is decompressed.
8. Recent or evolving cerebrovascular accident.
9. Multiorgan failure.
10. Metastatic tumors are an absolute contraindication.

F. Predictors of poor outcomes after implantation of LVADs

1. Age
2. RV failure
3. Urine output < 30 mL/h
4. Central venous pressure > 16 mm Hg
5. Receiving mechanical ventilation
6. Prothrombin time is > 16 seconds; vitamin K is usually given in high doses preoperatively to patients being considered for VAD
7. Reoperation
8. Cachexia syndrome

G. Echo-Doppler assessment of VAD dysfunction. After the implantation of LVAD, intraoperative transesophageal echocardiography is used to assess the following factors:

1. Position of the inflow cannula at the LV apex. If the cannula is angulated toward the interventricular septum, inflow obstruction may result. The velocity of the flow across the inflow cannula is affected by multiple factors, including the flow generated by the device. However, if this velocity is > 2 m/s, then obstruction of the cannula should be considered and thrombus or another mechanical cause of obstruction should be sought.
2. Adequacy of LV decompression.
3. Aortic valve. If the flow rate through the LVAD is adequate, the aortic valve should not open. If there is significant aortic regurgitation, the aortic valve may have to be replaced.
4. Doppler interrogation of the inflow and outflow cannulas is done to exclude inflow and outflow valve dysfunction. Usually, the valves are unable to open, resulting in increased forward flow velocities.
5. Periodic follow-up echocardiographic evaluation is performed to exclude thrombus formation, inflow cannula valve dysfunction, or endocarditis and to evaluate LV systolic function.

H. Right ventricular assist device (RVAD)

1. Decisions for RVAD support (needed by 20% of patients) are based on hemodynamics after LVAD placement. However, implantation of long-term RVAD

devices is more labor intensive and requires long bypass times for placement, which carries higher morbidity.

2. Univariate predictors of RVAD use are small BSAs, female gender, preoperative circulatory support, preoperative mechanical ventilation, and high total bilirubin and aspartate transferase values. Preoperatively, hemodynamic indices of a low mean or diastolic pulmonary artery pressure or a low RV stroke work index ($RVS_{WI} < 400 \text{ mm Hg} \cdot \text{mL/m}^2$) may indicate the necessity for RVAD after LVAD insertion.
3. Inotropic agents, volume infusions, and vasodilators are used to optimize pulmonary pressures and LVAD flows, with right heart hemodynamic values used as a guide. Aggressive diuresis is often necessary. If VAD flow remains $< 2 \text{ L/min/m}^2$, an RVAD system may be placed with the inflow from the right atrium and outflow to the pulmonary artery.
4. Inhaled nitric oxide has gained popularity as a potential alternative to RVAD implantation. In one center, it reduced the need for RVAD support from 7% to 0%.
5. However, the RVAD use is associated with higher incidence of repeat sternotomy for bleeding, and the survival to transplantation is poor at 17%. It may be prudent for patients with risk factors for RV dysfunction to receive a biventricular assist device or a TAH from the start.

I. Complications of VADs

1. **Perioperative bleeding** increases with prolonged cardiopulmonary bypass times and causes excess fibrinolysis and platelet consumption. The degree of bleeding is intimately associated with RV failure and RVAD support. Transfusion is associated with infection and human leukocyte antigen immunization, which can increase the risk of hyperacute humoral rejection for a patient who goes on to transplantation. The use of LVADs increases this risk from 4% to 25% because of the need for perioperative transfusions. Leukocyte-poor blood products should be used to minimize this risk as much as possible.
2. **Gastrointestinal bleeding** appears to be increased in continuous-flow LVADs in comparison with pulsatile ones, which is thought to be related to decreased levels of large multimers of von Willebrand factor and decreased platelet aggregation. Additional studies have also demonstrated increased incidence of arteriovenous malformations.
3. **Malignant arrhythmias.** There is a high incidence of malignant cardiac arrhythmia after device implantation. Causes include cardiomyopathy, ischemia, chamber dilation, use of inotropic agents, and focal abnormalities at the sewing ring.
4. **Infection.** Antibiotic prophylaxis should be administered to prevent infection. In the long term, there is a 25% to 45% rate of infection, which temporarily removes 20% of patients from the active transplantation list. The most serious infection is VAD endocarditis, which carries a 50% mortality rate and necessitates removal or replacement of the device.
5. **Embolic complications.** Thromboembolism still occurs at a high rate despite appropriate anticoagulation. The Thoratec device carries a 22% risk for cerebrovascular embolic events; the Novacor, 10%; and the HeartMate, 3% to 5% over a 1-year period.
6. **Aortic valve fusion and aortic insufficiency** may develop in patients with continuous-flow LVAD. In a small series of patients who received LVADs for bridge to transplant, examination of the explanted hearts demonstrated some degree of commissural fusion. Echocardiograms of those patients prior to explant demonstrated an increased incidence of aortic insufficiency during LVAD therapy. It is thought that the combination of valve fusion and continuous high pressure on the valve may contribute to the development of aortic insufficiency.

7. **RV failure** is responsible for significant morbidity and mortality after the institution of LVAD therapy. The complex pathophysiology resulting in RV failure includes RV myocardial dysfunction, changes in RV afterload, and inter-ventricular dependence. Risks for the development include biochemical signs of congestions (elevated total bilirubin and aspartate aminotransferase/alanine aminotransferase), decreased RVSWI, increased pulmonary vascular resistance, female gender, smaller patients, and pre-LVAD support. Therapies include inotropic support as well as right-sided mechanical support.
- J. **Bridging to transplantation.** Patients presenting with severe, refractory low cardiac output states need mechanical support as a bridge to transplantation. However, it has been recognized that major end-organ dysfunction affects the survival after transplantation. Mechanical support of the failing heart using short-term circulatory support devices can permit time to assess the reversibility of major organ dysfunction and allow a full workup for the suitability of cardiac transplantation. If the patient meets the selection criteria found in Table 12.2, full LVAD support can be implemented, and if the major organ dysfunction normalizes, a successful bridge to transplantation can be expected. It is expected that 70% to 80% of patients with an LVAD can be successfully bridged to transplantation, compared with 36% of patients managed on inotropic agents with or without an IABP, and 80% of these transplant patients will survive to be discharged from hospital. The percentage of transplant patients requiring mechanical support has increased steadily from 3% in 1990 to > 28% in 2004. Most LVAD implantations (75%) are performed with the strategy of bridge to transplantation. For those with biventricular failure that necessitates mechanical support, the options are combined RVAD and LVAD therapy or support with a TAH. The CardioWest TAH has been approved as a bridge to transplantation therapy.

TABLE 12.2 Patient Selection Criteria for Ventricular Assist Device Support as a Bridge to Cardiac Transplantation

1. Upper age consistent with successful cardiac transplantation, usually about age 70 y
2. Lower age limit determined by patient size large enough to accommodate a device
3. Suitable candidate for cardiac transplantation
4. Imminent risk of death before donor heart availability, usually with evidence of deterioration on maximal appropriate inotropic support and/or intra-aortic balloon support
5. General hemodynamic guidelines:
 - a. Cardiac index < 1.8 L/min/m²
 - b. Systolic arterial blood pressure < 90 mm Hg
 - c. Pulmonary arterial capillary wedge pressure > 20 mm Hg despite appropriate pharmacologic management
6. Adequate psychological criteria and external psychosocial support for transplantation and potentially prolonged LVAD support
7. Informed consent of patient or family
8. Absence of fixed pulmonary hypertension (pulmonary vascular resistance > 6 Wood units)
9. Absence of irreversible renal or hepatic failure (LVAD support not expected to reverse existing renal or hepatic dysfunction)

LVAD, left ventricular assist device.

Adapted from Kirklin JK, McGiffin D, Young JB. *Heart Transplantation*. New York, NY: Churchill Livingstone; 2002.

K. Bridging to recovery. Clinical recovery sufficient to allow mechanical support device removal has been reported in small numbers at a few institutions. In theory, chronic mechanical unloading may permit reverse remodeling with downregulation of collagen production and hypertrophy and decrease in circulating inflammatory cytokines. Likelihood of successful recovery is greater in those with acute nonischemic cardiomyopathy and much less likely in those with chronic dilated cardiomyopathy. Currently, approximately 5% of LVAD implantations are performed with the strategy of bridge to recovery.

ACKNOWLEDGMENTS: *The authors thank Drs. Bethany Austin, Kenneth Ng, and James O'Neill for their contributions to earlier editions of this chapter.*

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CHAPTER

13

Peter Zimbwa

Cardiac Transplantation

I. INTRODUCTION. Christiaan Barnard performed the first cardiac transplant in Cape Town in 1967. Since then, cardiac transplantation has become a well-established therapeutic option for a select group of patients with end-stage heart disease. It offers these patients, who have no other alternatives, a chance for extended survival and improved quality of life. Cardiac transplantation, however, should not be perceived as a curative procedure. Although the patient's primary problem of heart failure is alleviated by a successful transplantation, a new set of potential long-term complications arises primarily owing to the secondary effects of chronic immunosuppression.

Almost 89,000 heart transplants have been reported worldwide to the International Society for Heart and Lung Transplantation (ISHLT) registry since 1983 (1). As reporting to the ISHLT is voluntary, this number underestimates the actual number of cardiac transplants. There has, however, been a reduction in the number of annual heart transplants from a peak of > 4,000 in the mid-1990s to > 3,000 now. With an estimated additional 2,000 heart transplants per year not reported to the ISHLT, the total number of cardiac transplants likely exceeds 5,000 per year worldwide.

In the United States, the United Network for Organ Sharing (UNOS) reports a 10% reduction in cardiac transplantations over the same time period. UNOS is a national organization which, along with local organ procurement agencies, maintains organ transplantation waiting lists, initiates the evaluation of potential organ donors, allocates organs when a donor is identified, and compiles statistics annually on all aspects of the transplant process, including survival. Since 1990, the number of patients listed and waiting for a cardiac transplant in the United States has more than doubled. There is a shortage of donors, and each year 1.5 to 3 times as many patients are listed for cardiac transplantation as there are donors, so this problem is only going to escalate as the population gets older unless there is a significant increase in organ donation. The annual mortality rate while on the waiting list in 2001 was 15%, which has declined continually over the last decade, probably because of improved medical therapy for end-stage congestive heart failure and increased use of implantable cardioverter-defibrillator. As the annual number of cardiac transplantations has declined, wait times have continued to lengthen. The national median waiting time by UNOS status at listing from 2003 to 2004 data is as follows: 49 days for status 1A, 77 days for status 1B, and 308 days for status 2 patients. However, this can be misleading, as patients with different blood types such as blood type O wait significantly longer than other blood types such as blood type AB on average. A blood type O, status 2 patient could easily wait for > 2 years for a cardiac transplantation.

In the last 5 years (January 2005 to June 2009), the primary indication for adult cardiac transplantation has been nonischemic cardiomyopathies (53%), followed by ischemic cardiomyopathies (38%). Valvular heart disease (3%), adult congenital disease (3%), and retransplantation (3%) and miscellaneous causes (< 1%) account for the remainder (1). The average cardiac transplant recipient is male (77.1%), with an average age of 54 years, which reflects the demographics of the patients on the waiting list. The average donor age is 33 years, and donors > 50 years of age, which were rarely reported before 1986, now account for > 12% of all donors. Outcomes of transplantation continue to improve despite transplants performed on older, sicker patients. Recent data show that 44.5% of recipients were on intravenous inotropic support compared with 34% of recipients 10 years ago. Mechanical circulatory support is also more common, with > 31% of patients on some form of mechanical circulatory support at the time of transplantation, including 20.1% with a left ventricular assist device (LVAD) compared with only 15% on mechanical circulatory support (11% with an LVAD) 10 years ago (1). Survival rates post cardiac transplantation have improved from a median of 8.3 years in the 1980s to 13 years for those surviving to 1 year (1). The risk of death is highest in the first 6 months posttransplantation. Pretransplant factors associated with higher risk of mortality in the first posttransplant year include requiring mechanical circulatory support bridging to transplantation, congenital heart disease, and ischemic cardiomyopathy. Other risk factors include hemodialysis, mechanical ventilation, prior blood transfusion, and infection (1).

Because of the scarcity of donor organs and growing transplant waiting lists, it is crucial that cardiac transplant programs adequately screen and properly select potential transplant recipients. Effective use of this limited resource is essential to avoid “wasting” organs that become available for suboptimal recipients.

II. INDICATIONS FOR CARDIAC TRANSPLANTATION

- A. Patients should be on optimal medical therapy for congestive heart failure, as recommended by the American College of Cardiology/American Heart Association guidelines, including angiotensin-converting enzyme (ACE) inhibitor, digoxin, diuretic, β -blocker, and spironolactone. If a patient is intolerant to an ACE inhibitor, she or he should be on an angiotensin receptor blocker.
- B. Medically reversible causes of decompensated congestive heart failure should be excluded, including hypothyroidism, tachycardia-mediated cardiomyopathy, alcohol abuse, obstructive sleep apnea, hypertension, and medical noncompliance.

- C. Surgically reversible causes of decompensated congestive heart failure should be excluded, including valvular heart disease, unrevascularized coronary artery disease with large territories of ischemia or viability, hypertrophic obstructive cardiomyopathy, and LV (left ventricular) aneurysm for which resection would improve overall cardiac hemodynamics.
- D. Patients should be too ill or not candidates for cardiac resynchronization therapy. Alternatively, cardiac resynchronization therapy might have failed to improve symptoms or to halt progression of the underlying pathology.
- E. If the previous criteria are met, indications for a cardiac transplant evaluation are as follows:
 - 1. Cardiogenic shock requiring mechanical support (i.e., LVAD or intraaortic balloon pump counterpulsation)
 - 2. Cardiogenic shock requiring continuous intravenous inotropic therapy for hemodynamic stabilization
 - 3. New York Heart Association (NYHA) class III or IV congestive heart failure symptoms, particularly if progressively worsening
 - 4. Recurrent life-threatening LV arrhythmias despite an implantable cardiac defibrillator, antiarrhythmic drug therapy (usually amiodarone), or attempted catheter-based ablation, if appropriate
 - 5. End-stage complex congenital heart disease without pulmonary hypertension
 - 6. Refractory angina without potential medical or surgical therapeutic options

III. COMPONENTS OF A CARDIAC TRANSPLANT EVALUATION AND CONTRAINDICATIONS.

The purpose of a cardiac transplant evaluation is to exclude patients with medical and psychosocial comorbidities and to quantify the severity of a patient's cardiac functional impairment. Recommended investigations prior to a transplantation are summarized in Table 13.1 and exclusion criteria for cardiac transplantation are summarized in Table 13.2.

- A. **Blood work.** A standard blood work includes a complete blood cell count; a complete metabolic panel, including hepatic enzymes and thyroid function tests; and blood typing and antibody screening. A serologic assessment should also be performed to determine a potential recipient's presensitization to cytomegalovirus (CMV), toxoplasmosis, hepatitis B and C viruses, and human immunodeficiency virus (HIV).
 - 1. Patients who are anemic should have a thorough evaluation, including iron studies and a colon examination. Esophagogastroduodenoscopy and a hematologic evaluation, including a bone marrow biopsy, may also be necessary. Some patients may benefit from erythropoietin treatment to increase red blood cell counts without the need for transfusions that may expose the patient to further antigens.
 - 2. Patients found to have an elevated serum creatinine level should undergo further evaluation to determine its relationship with low renal perfusion. A normal urinalysis result suggests the absence of renal parenchymal disease. This should include an assessment of cardiac hemodynamics and a renal ultrasound to assess renal parenchymal size and the presence of two kidneys without evidence of obstruction.
 - 3. Patients found to have elevated hepatic enzymes should undergo further evaluation to determine the right-sided filling pressures and they should undergo a hepatic ultrasound scan. All patients should have their hepatitis B and C viral serologies assessed.
 - 4. The patient's serum should be screened for antibodies against human leukocyte antigen (HLA) of B and T lymphocytes, drawn from community volunteers representative of the major HLA allotypes. These antibodies are collectively referred to as panel reactive antibodies (PRAs) and are often elevated in multiparous women and patients with multiple transfusions (often perioperatively in the past). Elevated PRA levels (> 10%) necessitate a pretransplant donor HLA crossmatch

TABLE 13.1 Recommended Evaluation prior to Transplantation

Complete history and physical examination

Laboratory investigations:

Complete blood count with differential and complete metabolic panel

Thyroid function studies (thyroid-stimulating hormone)

Liver function panel, creatinine clearance

Lipid profile, hemoglobin A1c, and urinalysis

Immunologic data:

Blood type and antibody screen

Human leukocyte antigen typing

Panel reactive antibodies' screen

Serology for infectious diseases:

Hepatitis (HBsAg, HBsAb, HBcAb, and HepCAb)

Herpes group virus

Human immunodeficiency virus

Cytomegalovirus IgG antibody

Toxoplasmosis

Varicella and rubella titers

Epstein-Barr virus IgG and IgM antibodies

Venereal Disease Research Laboratory or Rapid Plasma Reagin

Cardiovascular investigations:

Electrocardiogram, chest X-ray, and echocardiogram

Exercise test with oxygen consumption

Right and left heart catheterization

Myocardial biopsy (if indicated, e.g., to rule out infiltrative process such as amyloidosis)

Vascular assessment:

Carotid Doppler

Peripheral vascular assessment (ankle-brachial index and/or duplex ultrasound)

Abdominal ultrasound

Ophthalmology examination (if indicated, e.g., to rule out diabetic retinopathy)

Cancer screening:

Prostate-specific antigen (in men if indicated)

Papanicolaou smear and mammography (in women if indicated)

Colonoscopy (if indicated)

Psychosocial evaluation:

Support system

Substance abuse history (alcohol, tobacco, and drug use)

Psychiatric history

Baseline investigations:

Dental examination

Bone density scan

Pulmonary function tests

TABLE 13.2 Exclusion Criteria for Cardiac Transplantation

Irreversible pulmonary parenchymal disease
Renal dysfunction with Cr > 2.0–2.5 or CrCl < 30–50 mL/min (unless for combined heart-kidney transplant)
Irreversible hepatic dysfunction (unless for combined heart–liver transplant)
Severe peripheral and cerebrovascular obstructive diseases
Insulin-dependent diabetes with end-organ damage
Acute pulmonary embolism
Irreversible pulmonary hypertension (PVR > 4.0 Wood units after vasodilators)
Psychosocial instability or substance abuse
History of malignancy with probability of recurrence
Advanced age (> 70 y)
Severe obesity
Active infection
Severe osteoporosis

PVR, pulmonary vascular resistance.

and increase the likelihood of it being positive, making waiting times longer and transplantation more difficult. If a patient has elevated PRA levels, an attempt to reduce them before transplantation with intravenous immunoglobulin, plasmapheresis, mycophenolate mofetil (MMF), or cyclophosphamide, alone or in combination, may be considered. Traditionally, each potential recipient would undergo a thorough HLA tissue typing analysis, including a cytotoxicity assay for assistance in matching donor hearts. In this assay, random donor lymphocytes are incubated with recipient sera. Complement-dependent antibody-mediated cytotoxicity identifies potential donor-specific antibodies present in that recipient. Currently, most programs use flow cytometry to assess preformed antibodies, rather than cytotoxic assays. This allows for the detection of weaker interactions and provides a wider, more efficient screening process.

B. Imaging

1. All patients should undergo coronary angiography or a functional assessment for ischemia and viability. If ischemia or viability can be demonstrated, consideration should be given to percutaneous or surgical revascularization.
2. Bilateral carotid ultrasound scans should be performed in patients with risk factors for atherosclerosis. Select patients with carotid stenoses, who would otherwise be cardiac transplant candidates, may undergo pretransplantation percutaneous or surgical intervention, thereby eliminating this contraindication.
3. Occasionally, an abdominal aortic ultrasound is obtained to rule out an aneurysm, particularly in patients being considered for mechanical support.

C. Functional assessment

1. Metabolic stress testing is performed to assess the severity of cardiac functional impairment. Patients with compensated congestive heart failure and a peak oxygen consumption of < 14 mL/kg/min or < 50% predicted are considered sufficiently impaired for transplantation (2). Adequate patient effort during the stress test can be assessed by the respiratory exchange ratio, which should be > 1.1, indicating the onset of anaerobic metabolism.

2. Generally, a right heart catheterization is performed to assess cardiac hemodynamics and to optimize a patient's medical therapy. Fixed, severe pulmonary hypertension, defined as a pulmonary vascular resistance (PVR) > 4 Wood units, is a contraindication to cardiac transplantation. In this setting, the donor right ventricle will likely immediately fail after implantation because it is not accustomed to high pulmonary pressures. An attempt should be made to medically decrease the pulmonary hypertension with inotropic agents, nitrates, or nitroprusside. Sometimes an LVAD is required to sufficiently decompress the left ventricle to reverse the pulmonary hypertension. Rarely, endomyocardial biopsy (EMB) is performed, except when an infiltrative cardiomyopathy is suspected.
 3. Pulmonary function tests are performed to exclude patients with significant chronic obstructive or restrictive pulmonary disease.
 4. Peripheral vascular studies may be obtained to exclude patients with significant peripheral arteriosclerosis obliterans.
- D. Comorbidities and implications of heart transplant listing.** Advanced age, cancer, and obesity are the three common comorbidities that remain somewhat controversial with respect to their impact on whether an individual program will list a patient for heart transplantation.
1. Age criteria for eligibility were initially quite rigorous; however, it has become apparent that **chronologic and physiologic age are often discrepant**. Most centers do not have a fixed upper age limit, but generally patients > 65 years of age are very carefully screened to rule out comorbidities. ISHLT recommends considering patients for cardiac transplantation if they are ≤ 70 years of age (3). Patients > 70 years of age may be considered for cardiac transplantation at the discretion of the transplant program and should theoretically be in excellent health except for heart disease. An alternate type of program has been proposed for these patients, whereby older donor hearts would be utilized in this population (3).
 2. Active **malignancy** other than skin cancer is an absolute contraindication to cardiac transplantation due to limited survival rates. Chronic immunosuppression is associated with a higher than average incidence of malignancy and is associated with increased recurrence of prior malignancy. Patients with cancers that have been in remission for ≥ 5 years and patients with low-grade cancers such as prostate cancer are generally accepted for transplant evaluation. Preexisting malignancies are heterogeneous in nature and some are readily treatable with chemotherapy. Thus an individualized approach to these patients is required, and consultation with an oncologist regarding prognosis is often very helpful.
 3. Traditionally, centers have been cautious when considering **obese** patients for transplantation. Most currently available data indicate that patients with a pre-transplant body mass index (BMI) > 30 kg/m² have poor outcomes following cardiac transplantation, with increased rates of infection and higher mortality rates. However, this area remains controversial and some recent data presented in abstract form only demonstrate no significant mortality differences between obese (BMI, 30 to 34.99) transplant recipients and overweight (BMI, 25 to 29.99) transplant recipients. Despite this controversy, the current ISHLT recommendations are that patients achieve a BMI < 30 kg/m² or a percent ideal body weight $< 140\%$ prior to being listed for cardiac transplantation (3). This cutoff will vary from center to center, but generally a BMI > 35 kg/m² will preclude listing for cardiac transplantation.
- E. Consultations**
1. A **psychosocial assessment** is a crucial component of every cardiac transplant evaluation. Accepted psychosocial contraindications for cardiac transplantations include active smoking; active substance abuse, including alcohol; medical noncompliance; and significant untreated psychologic or psychiatric diagnoses.

Relative psychosocial contraindications to cardiac transplantation include post-traumatic stress disorder and lack of an adequate support structure.

2. For **diabetic patients, an ophthalmology consultation** is obtained for an assessment of retinal end-organ damage related to the diabetes.

IV. UNOS AND THE RECIPIENT LIST. After a patient is accepted as a potential cardiac transplant recipient by a UNOS-certified transplant program, the patient's name is entered on a national list compiled by UNOS. The patient is given a status level based on predefined clinical criteria (Table 13.3), which can be adjusted as the patient's clinical situation evolves. A patient's priority on the UNOS list depends on his or her status level and the duration of time on the list. **Highest priority is given to patients with status 1A and those who have been waiting the longest.** A critical patient initially listed as status 1A immediately has a higher priority than a patient with a status 1B, regardless of the duration of time spent as status 1B. Whether a patient is hospitalized or not does not affect priority on the list, other than the fact that hospitalized patients are more likely to be receiving hemodynamic support (mechanical or inotropic) and are

TABLE 13.3 Description of Status Levels in the United Network of Organ Sharing List

Status	Description
1A	<p>Must be an inpatient</p> <p>Life expectancy < 7 d</p> <p>LVAD and/or RVAD (maximum 30 d)</p> <p>VAD-related thromboembolism</p> <p>VAD-related infection (including the pocket and the driveline)</p> <p>Mechanical failure of VAD</p> <p>Total artificial heart</p> <p>Extracorporeal membrane oxygenation</p> <p>Intraaortic balloon pump with inotropic criteria</p> <p>Life-threatening refractory arrhythmias with or without a VAD</p> <p>Mechanical ventilation</p> <p>High-dose single intravenous inotrope (see doses below) or multiple intravenous inotropes, in addition to Swan-Ganz catheter</p>
1B	<p>Inotrope-dependent</p> <p>VAD not meeting criteria for 1A status</p>
2	Not inotrope-dependent
7	Inactive on list because of improved clinical status or short-term contraindications to cardiac transplantation (e.g., active infection)
Inotrope criteria for status 1a	
1.	Two or more inotropes, regardless of dose
2.	Intravenous milrinone, at least 0.5 µg/kg/min by continuous infusion
3.	Intravenous dobutamine, at least 7.5 µg/kg/min by continuous infusion

LVAD, left ventricular assist device; RVAD, right ventricular assist device; VAD, ventricular assist device.

at a higher status level. A hospitalized patient on continuous inotropic therapy has the same status as a similar patient on home continuous inotropic therapy. Patients on home continuous inotropic therapy awaiting cardiac transplantation are generally thought to have an increased mortality related to the proarrhythmic effect of inotropic therapy, and most programs require implantation of an intracardiac defibrillator as a prerequisite for discharge.

V. WORKUP OF A POTENTIAL CARDIAC DONOR. Potential cardiac donors are patients who are declared brain dead but otherwise have viable internal organs. Generally, these are patients with lethal head injuries or catastrophic central nervous system events (i.e., intracranial hemorrhage, stroke, or cerebral anoxia).

A. Declaration of brain death. A neurologist or a neurosurgeon usually declares the brain death of a potential organ donor. Usually, this declaration is made after a period of observation (about 12 hours) during which no neurologic improvement is seen. Physicians involved in the care of potential transplant recipients are not involved in this decision to avoid conflicts of interest. Criteria for the determination of brain death are very specific. Absence of any one of the following criteria makes the patient ineligible for organ donation.

- (1) A known cause of death
- (2) Absence of hypotension, hypothermia, hypoxemia, and metabolic perturbations
- (3) Absence of medical or recreational drugs known to depress the central nervous system
- (4) Absence of cerebral cortical function
- (5) No response to painful stimuli
- (6) Absence of brainstem reflexes
 - (a) Pupillary constriction to light
 - (b) Corneal reflex
 - (c) Vestibular ocular reflexes (i.e., doll's eyes or cold caloric testing)
 - (d) Gag reflex
 - (e) Cough reflex
- (7) Positive apnea test: no spontaneous respiration despite arterial $\text{PCO}_2 > 60$ mm Hg for at least 10 minutes after disconnection from the ventilator
- (8) An electroencephalogram (EEG) is not required but may be performed at the discretion of the examining physician. The EEG should demonstrate electrical silence.

B. Potential donor screening. After a patient is declared brain dead, a local organ procurement organization (OPO), under the auspices of UNOS, performs the initial evaluation of a potential donor. This evaluation includes a thorough patient and family history, focusing specifically on cardiac risk factors and potentially transmissible diseases (i.e., malignancy and infection). Preliminary blood tests are done, including determinations of cardiac enzymes; serologies for hepatitis B and C viruses, HIV, toxoplasmosis, and CMV; ABO blood group typing; and HLA antigen typing. An echocardiogram is routinely performed to assess the cardiac function and to rule out congenital anomalies and valvular disease. At the request of the potential recipient's physician, a coronary angiogram may be obtained if a donor has significant cardiac risk factors, has positive cardiac enzymes, or is relatively advanced in age. Cardiac donor selection criteria are summarized in Table 13.4.

If the potential recipient also has elevated PRA levels, a prospective complement-dependent antibody-mediated lymphocytotoxic crossmatch is usually performed, in which the recipient's serum is incubated with donor lymphocytes to identify potential donor–recipient HLA incompatibility. Many centers today perform a “virtual crossmatch” for patients with elevated PRA levels to improve donor availability. With the HLA technologies available today, the exact antigen specificity of the recipients' anti-HLA antibodies is known. If the HLA tissue typing of the potential donor

TABLE 13.4 Cardiac Donor Selection Criteria

Must meet legal requirements for brain death
No history of chest trauma or cardiac disease
No prolonged hypotension or hypoxemia
Normal ECG
Normal cardiac angiogram, performed if indicated by donor age (male > 45 y or female > 50 y) and history
Negative HBsAg, hepatitis C virus, and human immunodeficiency virus serologies
Systolic blood pressure > 100 mm Hg or mean arterial pressure > 60 mm Hg
Central venous pressure 8–12 mm Hg
Inotropic support < 10 µg/kg/min dopamine or dobutamine
Age < 55 y preferred

ECG, electrocardiogram.

does not include the antigens against which the recipient is sensitized, it is assumed that the actual crossmatch will be negative (i.e., a “virtual” negative crossmatch). If a prospective crossmatch is not performed, a retrospective crossmatch (by lymphocytotoxic assay or by flow cytometry) is performed using donor lymphocytes obtained from donor aortic lymph nodes retrieved at the time of harvest.

- C. Donor–recipient matching.** UNOS maintains a computerized list of all patients listed and waiting for cardiac transplantation. A list of potential recipients with compatible blood types is generated for each potential donor organ and is made available to the OPO. In this list, priority is given to local patients (defined as within the OPO’s territory) with the highest status level who have been waiting the longest. Recent changes to the UNOS donor net criteria mean that a local status 2 patient is no longer higher on the list than a status 1A patient from outside the OPO’s territory.

Transplant physicians of the potential recipient may also reject a potential organ because of a positive prospective crossmatch, donor–recipient size mismatch, or a prolonged projected ischemic time (usually related to long-distance travel). Matching donor and recipient size is important, because an oversized donor organ may not allow closure of the chest without compression of the organ and an undersized donor organ may not be able to pump a sufficient quantity of blood. **Current guidelines suggest that the recipient’s weight should range between 70% and 130% of a potential donor’s weight (4).**

- VI. SURGICAL ISSUES RELATED TO CARDIAC TRANSPLANTATION.** Most surgical issues related to cardiac transplantation are beyond the scope of this chapter and are mainly of interest to the cardiac surgeon. The main surgical issue of interest to the transplant cardiologist is related to the anastomosis of the right atrium. The surgeon may suture the donor atrium to the recipient atrium (i.e., **biatrial anastomosis**) or suture the donor superior vena cava to the recipient superior vena cava and the donor inferior vena cava to the recipient inferior vena cava (i.e., **bicaval anastomosis**). The bicaval anastomosis approach is more time consuming but reduces the incidence of atrial arrhythmias (including sinus

node dysfunction), reduces the incidence of posttransplant tricuspid regurgitation, and improves right atrial hemodynamics. The bicaval anastomosis approach does, however, provide some potential difficulties to the cardiologist trying to perform surveillance EMBs, because these anastomoses have a tendency to scar and narrow the central lumen over time. Currently, most centers employ the bicaval anastomosis approach, although no survival advantage has been conclusively demonstrated with this approach.

VII. POSTOPERATIVE COMPLICATIONS AFTER CARDIAC TRANSPLANTATION

A. Surgical complications. The most common surgical complication is the development of a **pericardial effusion** with or without tamponade. Pericardial effusions are very common because of the large potential space left behind as the dilated and dysfunctional recipient left ventricle is replaced with a more appropriately sized donor left ventricle. Rarely, pericardial tamponade develops, necessitating percutaneous or surgical evacuation of the pericardium. Other surgical complications are much less common but can be catastrophic and usually result from a problem either at a site of anastomosis or at a site of cannulation.

B. Early graft dysfunction

- 1. LV systolic dysfunction.** It is common for transplant recipients to require inotropic support as they come off cardiopulmonary bypass. The most commonly used inotropic agents in this setting are dobutamine, milrinone, and isoproterenol, used alone or in combination. It is also common for transplant recipients to require peripheral vasoconstrictors such as epinephrine, norepinephrine, and dopamine in the early postoperative period, because most are on large quantities of oral or intravenous vasodilators before transplantation. Most patients can be weaned off inotropic therapy and peripheral vasoconstrictors within the first 48 hours.
 - 2. LV diastolic dysfunction** is very common soon after cardiac transplantation. It usually results from reversible ischemia or reperfusion injury to the donor organ and normally resolves over a period of days to weeks. If the ischemia or reperfusion injury is sufficiently severe to induce significant contraction band necrosis or myocardial fibrosis, as seen on EMB, chronic diastolic dysfunction can ensue. Another potential cause of diastolic dysfunction is donor–recipient mismatch, particularly with a small donor organ or acute rejection.
 - 3. Right ventricular dysfunction** is much more common than LV dysfunction after cardiac transplantation, especially in patients with preexisting pulmonary hypertension. The right ventricle is subjected to similar ischemic or reperfusion injury risks as the left ventricle. Right ventricular dysfunction is usually accompanied by right ventricular dilation and the failure of coaptation of the tricuspid valve leaflets, leading to severe tricuspid regurgitation. The treatment for perioperative right ventricular dysfunction is usually intravenous milrinone and nitrates to increase cardiac output and lower the PVR. In patients with refractory pulmonary hypertension, other agents to be considered include nitroprusside, nesiritide, isoproterenol, or rarely, inhaled nitric oxide. Usually, the pulmonary hypertension and right ventricular dysfunction improve over a period of days to weeks.
- C. Cardiac arrhythmias.** Most transplant recipients require perioperative temporary atrioventricular pacing. Sinus node dysfunction is very common, probably because of a combination of surgical trauma, ischemia or reperfusion injury, and denervation. The incidence of sinus node dysfunction is believed to be reduced by the bicaval anastomosis technique compared with the biatrial anastomosis technique. With time, the sinus node usually recovers, and a permanent pacemaker is unnecessary. Preoperative use of amiodarone increases the likelihood of bradycardia after transplantation. Other cardiac arrhythmias are rare, especially off inotropic therapy, and may signify acute rejection.
- D. Renal dysfunction.** Preoperatively, many transplant recipients have some degree of impaired renal function. There is a risk of worsening renal function perioperatively.

This risk is compounded by the fact that the major immunosuppressive agents (i.e., cyclosporine and tacrolimus) are nephrotoxic. If renal function does worsen postoperatively, induction therapy is begun to delay initiation of cyclosporine or tacrolimus. Most centers no longer use OKT3 for induction therapy but rather use interleukin-2 (IL-2) receptor blockers or thymoglobulin for induction therapy.

VIII. SYSTEMIC IMMUNOSUPPRESSION. Much of the success in cardiac transplantation today is attributed to advances in immunosuppression. However, balancing the risk of allograft rejection against the inherent risk of immunosuppression remains a challenge in transplant medicine. Immunosuppressant protocols during and after cardiac transplantation vary greatly from program to program and even from patient to patient within a program. Triple therapy, which constitutes the cornerstone of modern immunosuppressive regimens in cardiac transplantation, including a calcineurin inhibitor (such as cyclosporine or tacrolimus), a cell cycle–modulating or antiproliferative agent (such as MMF or azathioprine), and a corticosteroid (4), is increasingly being challenged. Recently, the Tacrolimus in Combination, Tacrolimus Alone Compared (TICTAC) trial prospectively randomized 150 cardiac transplant patients in an open fashion to receive either tacrolimus monotherapy or tacrolimus and MMF. Corticosteroids were used in all patients but were successfully discontinued over 8 to 9 weeks. The addition of MMF to tacrolimus did not provide an advantage over tacrolimus alone in terms of primary end point of rejection over the first 6 months, the secondary end points of allograft vasculopathy, and 3-year survival (5). The trial has, however, been criticized for being underpowered to demonstrate true differences in the primary and secondary end points, its use of an unvalidated biopsy grading scale, inconsistent timing of intravascular ultrasound (IVUS), use of higher and potentially nephrotoxic levels of tacrolimus, and the lack of a control arm of routine triple drug immunosuppression for comparison with the two study arms (6). Controversy remains about the advisability of using cytolytic or induction therapy in the nonpresensitized recipient without renal failure (Table 13.5).

A. Steroids. The mechanism by which steroids serve as immunosuppressants is complex and incompletely understood. Steroids bind to nuclear receptors, thereby preventing gene expression of various cytokines important for B-cell and T-cell activation and proliferation, the most important of which is IL-2. Steroids also have important anti-inflammatory properties and suppress macrophage activity. Important side effects of steroids include diabetes, hypertension, weight gain, osteoporosis, and avascular necrosis of the femoral head.

Steroid-dosing protocols vary tremendously from one institution to another. A dose of 500 to 1,000 mg of intravenous Solu-Medrol is usually given to the patient before being brought to the operating room and then 125 to 150 mg is usually repeated every 8 hours for a total of three more doses. At that point, if the patient is extubated, oral prednisone is begun. Some centers start at a divided dose of 1 mg/kg/d and wean by 5 mg daily, whereas others start immediately at only 20 mg daily. The dose of steroid is slowly tapered, provided the patient continues to have a clean biopsy record. The trend in clinical practice is to wean most patients completely off steroids. Some centers continue to advocate the indefinite use of low-dose prednisone (2.5 to 5 mg daily). If a decision is made to withdraw steroids completely, it should be done approximately 1 month before the next scheduled biopsy to ensure continued lack of acute cellular rejection.

Steroids are also given in “pulses” to treat episodes of acute cellular rejection. If a patient has acute cellular rejection associated with hemodynamic compromise, she or he is admitted for 1 g of intravenous Solu-Medrol daily for 3 days and may be given cytolytic therapy or plasmapheresis, or both. If no hemodynamic compromise is associated with the episode of rejection, a daily dose of 100 mg oral prednisone for 3 days is usually sufficient, followed by repeat biopsy, at most 2 weeks later to ensure resolution.

TABLE 13.5

Common Immunosuppressants

	Steroids	Calcineurin inhibitors	MMF	AZA	TOR inhibitors	OKT3	Polyclonal antilymphocyte antibodies	IL-2 receptor blockers
Drugs	Prednisone (P) (po)	Neoral (N)	—	—	Rapamycin (R)	—	Atgam (A)	Basiliximab (B)
	Solu-Medrol (S) (IV)	Tacrolimus (T)	—	—	Everolimus (E)	—	Thymoglobulin (T)	Daclizumab (D)
Indication	Chronic IM, acute rejection	Chronic IM	Chronic IM, skin cancer with AZA	Chronic IM	Chronic IM, vasculopathy	Induction, acute rejection	Induction, acute rejection	Induction
Dosing								
Initial	IV 125–150 mg q8h	N: 100 mg bid T: 2 mg bid	1.5 g bid	1–2 mg/kg/d	R: 2–5 mg qd E: 1.5–3 mg qd	—	—	—
Induction	—	—	—	—	—	5 mg qd × 5–15 d	A: 15 mg/kg/d T: 1.5 mg/kg/d × 5–15 d	B: 20 mg on days 1 and 4 D: 1 mg/kg q1–2wk × 5 doses
Maintenance	Weaned off	Adjusted to levels	1.5 g bid	1–2 mg/kg/d	Adjusted to levels	—	—	—
Acute rejection	P: 100 mg qd × 3 S: 1 g IV qd × 3	Consider change from CsA to tacrolimus	—	—	—	As above	As above	—

Target levels	—	See Tables 12.3 and 12.4	2–4 ng/mL, 12-h trough, WBC > 4.0	WBC > 3.0	R: 4–12 ng/mL, 18-h trough	CD3 count < 20 cells/mL	CD3 count < 20 cells/mL	—
Common side effects	Diabetes, osteoporosis, weight gain, hypertension, and adrenal insufficiency	Nephrotoxicity, hypertension, tremors, and gingival hyperplasia	Diarrhea, nausea, and myelosuppression	Myelosuppression, skin cancer	Hypertriglyceridemia and thrombocytopenia	Cytokine release, hypotension, capillary leak syndrome, and CMV superinfection	Thrombocytopenia, fevers, chills, PTLD, and CMV superinfection	—
Common drug interactions	—	Erythromycin, diltiazem, verapamil, rapamycin, anticonvulsants, rifampin, and statins	Cholestyramine and probenecid	Allopurinol	Cyclosporine	—	—	—

AZA, azathioprine; CMV, cytomegalovirus; CsA, cyclosporin A; IL, interleukin; IM, immunosuppression; MMF, mycophenolate mofetil; PTLD, posttransplant lymphoproliferative disorder; TOR, target of rapamycin.

B. Calcineurin inhibitors. Calcineurin is a phosphatase enzyme that triggers transcription of new messenger RNA after activation of the T-cell receptor by an appropriate antigen, leading to increased gene expression of IL-2 and other important cytokines. Calcineurin antagonists inhibit this phosphatase activity, thereby preventing the synthesis of these cytokines, which prevent B-cell and T-cell proliferation.

1. Cyclosporine (Neoral, Gengraf, and Sandimmune) is a calcineurin antagonist with a highly variable pattern of bioavailability, depending on the oral formulation taken. Bioavailability of the original soft gelatin capsule (Sandimmune) was low and depended on emulsification by bile salts. The newer microemulsion formulation (Neoral) does not depend on bile salts for emulsification and has a more consistent bioavailability. Nevertheless, there remain tremendous interpatient differences in bioavailability, and dosing of Neoral is primarily based on serum drug trough levels. Because of the narrow therapeutic range of cyclosporine, drug trough levels are also important to prevent toxicity. Nephrotoxicity is the most important side effect of cyclosporine therapy and is related to renal afferent arteriolar vasoconstriction and the resultant reduced renal perfusion. Other side effects include systemic hypertension, gingival hyperplasia, and tremors. Calcium channel blockers, particularly diltiazem, reduce hepatic metabolism of cyclosporine, thereby increasing serum drug levels. This drug interaction is frequently used clinically to reduce the oral dose of cyclosporine required to achieve a given serum drug concentration, thereby minimizing the cost of immunosuppression.

Postoperatively, once the patient is hemodynamically stable with good urine output, cyclosporine is initiated via continuous infusion at 1 mg/h. When the patient is able to take oral medicines, Neoral is begun at a dose of 100 mg twice daily, with adjustments in the dose based on serum trough levels (Table 13.6). The dose of Neoral is gradually reduced over a period of 1 year if the patient has a clean biopsy record.

2. Tacrolimus (Prograf), previously known as FK506, is another calcineurin inhibitor that has low oral bioavailability. Tacrolimus has never been prospectively shown to be superior to cyclosporine in the prevention of acute cellular rejection. However, it has become a standard practice to change cyclosporine in a patient's immunosuppressive regimen to tacrolimus in the setting of recurrent or persistent acute cellular rejection with adequate cyclosporine levels. Some programs empirically use tacrolimus for all female patients because a common side effect of cyclosporine is hirsutism. The major side effects of tacrolimus are nephrotoxicity and neurotoxicity (most commonly tremor).

Like cyclosporine, tacrolimus is initiated postoperatively once the patient is hemodynamically and renally stable. A dose of 0.01 mg/kg/d of tacrolimus is administered by continuous infusion. Unfortunately, intravenous tacrolimus is seemingly more nephrotoxic than cyclosporine. Tacrolimus can be given sublingually using an oral to sublingual dose ratio of 1:1. After the patient starts taking

TABLE 13.6 Target Serum Cyclosporin A Levels

Time	Target level (12-h trough)
0–3 mo	250–350 ng/mL
3–12 mo	200–250 ng/mL
>12 mo	150–175 ng/mL

TABLE 13.7 Target Serum Tacrolimus (FK506) Levels

Time	Target level (12-h trough)
0–30 d	12–20 ng/mL
1–6 mo	8–15 ng/mL
6–18 mo	5–15 ng/mL
>18 mo	5–10 ng/mL

medicines orally, the dosage of tacrolimus is changed to 0.5 to 2 mg twice daily, with dose adjustment based on serum FK506 levels (Table 13.7).

- C. Mycophenolate mofetil (CellCept).** MMF inhibits DNA synthesis by inhibiting de novo purine synthesis. Because human lymphocytes depend on the de novo synthesis of purines for DNA replication, MMF has the unique ability to inhibit B-lymphocyte and T-lymphocyte proliferation without affecting DNA synthesis in other cell lines, which can obtain purines through the parallel and unaffected purine salvage pathway. MMF has become the preferred immunosuppressant over azathioprine at most transplant centers because of a reduced mortality rate at 1 year (6.2% vs. 11.4%; $p = 0.03$), especially among patients with treated biopsy-proven rejection and severe hemodynamic compromise (32% vs. 0%). Although there is a trend toward a reduced incidence of grade 3A (now 2R) rejection in MMF-treated patients compared with azathioprine-treated patients, it did not reach statistical significance (45% vs. 52.9%; $p = 0.055$). The main disadvantage of MMF over azathioprine is the increased cost (almost 10-fold) and the potential increased risk of opportunistic viral infections. Toxicities of MMF include gastrointestinal symptoms (nausea, vomiting, and diarrhea) and myelosuppression. Some patients on MMF develop clinically significant leukopenia, necessitating dose reduction or discontinuation of the drug. The incidence of these adverse events is higher in patients receiving > 3 g/d of MMF. Most symptoms will resolve with the reduction of dose.

MMF is given intravenously or orally. Because of the high bioavailability ($> 90\%$), the initial dose of MMF is 1 g taken twice daily, regardless of the route of administration. The initial dose is given within the first 12 hours after transplantation. Few centers monitor the serum levels of mycophenolic acid (MPA), the active metabolite of MMF. The serum levels of MPA are higher when MMF is administered with tacrolimus compared with cyclosporine; therefore, it may be advisable to empirically reduce the dosage of MMF when switching from cyclosporine to tacrolimus. Although there is no consensus on dose adjustment of MMF, at the Cleveland Clinic, the dose is adjusted to maintain MPA 12-hour trough concentrations in the range of 2 to 4 $\mu\text{g/mL}$.

- D. Azathioprine (Imuran)** is a purine analog that impairs DNA synthesis, thereby preventing B-lymphocyte and T-lymphocyte proliferation in response to antigen stimulation. Azathioprine has largely been replaced by MMF as the antiproliferative agent of choice in the triple immunosuppressant cocktails of today. Because there is no drug level assay available, azathioprine dosing is usually fixed between 1 and 2 mg/kg/d. The major side effect of azathioprine is myelosuppression, and the dose of azathioprine is usually adjusted to maintain a white blood cell count of $> 3,000/\text{mL}$. Azathioprine is metabolized by xanthine oxidase, and xanthine oxidase inhibitors such as allopurinol can lead to the accumulation of toxic levels of azathioprine and profound and prolonged myelosuppression.

E. Inhibitors of the target of rapamycin (TOR) enzyme: sirolimus (Rapamune) and everolimus (Certican, previously known as RAD). Immunosuppressants have been developed that inhibit the enzyme TOR. TOR is activated after IL-2 stimulation of the T-cell IL-2 receptor and is critical for lymphocyte growth and proliferation. In contrast to calcineurin inhibitors, inhibitors of TOR do not block cytokine production (e.g., IL-2) but rather block the cellular response to these cytokines. TOR inhibitors also inhibit vascular smooth muscle cell growth and proliferation in response to various growth factors. It is hoped that this property of TOR inhibitors will help reduce the rate of progression of chronic transplant coronary vasculopathy. Unlike calcineurin inhibitors, TOR inhibitors are not nephrotoxic. When used in combination with cyclosporine, TOR inhibitors appear to act synergistically with regard to immunosuppression. However, worsening of renal function is common but can be prevented by lowering the cyclosporine dose without worsening of immunosuppression. The main side effects of this class of compounds are significant hypertriglyceridemia and thrombocytopenia.

Sirolimus and everolimus are both TOR inhibitors. They are structurally similar, but everolimus has a much higher bioavailability than sirolimus. The appropriate dosing of these agents remains unclear, but for sirolimus, it is probably 1 to 5 mg/d, and for everolimus, it is probably 1.5 to 3 mg/d. Sirolimus appears to lower the incidence of acute cellular rejection in humans (7) and to slow the progression of transplant vasculopathy (8). Preliminary human studies using intravascular coronary ultrasonography have also shown a reduction in neointimal proliferation with both sirolimus and everolimus.

It remains unclear where TOR inhibitors will fit in with current immunosuppressive protocols. The most likely scenario is their use in combination with a calcineurin inhibitor and prednisone, in place of MMF or azathioprine. Alternatively, they could be used in place of calcineurin inhibitors and in combination with MMF or azathioprine and prednisone, particularly in patients with either preexisting or worsening renal dysfunction.

F. Induction therapy and therapy for steroid-resistant acute rejection. The purpose of induction therapy is to deplete T lymphocytes or to prevent lymphocyte proliferation during the most immunoreactive phase, which occurs immediately after transplantation. Induction therapy has continued to be a subject of controversy in heart transplantation for more than 20 years. Induction therapy is not routinely used in posttransplant patients because of a lack of evidence of improved survival or less acute rejection. The two clear indications to use induction therapy are as follows: (1) in patients who have severe renal dysfunction, which precludes the introduction of calcineurin inhibitors within the first 2 days following transplantation and (2) in patients who have acute graft failure secondary to an immune mechanism such as with hyperacute rejection or humoral rejection. The two scenarios in which induction therapy is often used are in patients with preexisting significant renal dysfunction and in significantly presensitized patients.

The principle behind the treatment of steroid-resistant acute rejection is similar, in that the depletion of activated T lymphocytes presumably prevents further clonal expansion of the antigen-activated offending lymphocyte population.

1. OKT3 (Muromonab-CD3) is a murine-based monoclonal anti-CD3 antibody. The CD3 antigen is part of the T-cell receptor complex present on activated, circulating T lymphocytes. OKT3 binds to the CD3 antigen and produces cell death by multiple mechanisms or T-cell receptor internalization, thereby inactivating the lymphocyte.

The dose of OKT3 is 5 mg/d, for a total of 5 to 10 days. After a course of OKT3, there is an immediate and well-recognized rebound in CD3-positive (activated) T-lymphocyte counts that can lead to acute cellular or humoral rejection. Cytokine release syndrome frequently occurs and typically begins 30 to 60 minutes after administration of a dose of OKT3 and may persist for

several hours. Premedication with acetaminophen, steroids, and antihistamines may help minimize symptoms. CD3+ T cells are generally undetectable during OKT3 therapy; however, within 12 to 24 hours after cessation of OKT3, CD3+ T cells reappear in circulation, unlike after treatment with antithymocyte globulin (ATG) preparations, with which the lymphocyte depletion is present for weeks. Therefore, many programs prophylactically increase the steroid dose during withdrawal from OKT3. Since OKT3 is a murine-based monoclonal antibody, patients may develop antibodies toward the mouse component of the antibody that may limit the effectiveness of future courses of OKT3. Patients treated with OKT3 have had an increased incidence of posttransplant lymphoproliferative disorder (PTLD) and lymphoma with a cumulative dose of > 75 mg. Opportunistic viral infections are also more common after OKT3 therapy.

2. **Polyclonal antilymphocyte antibodies** are produced by injecting animals with human lymphocytes or thymocytes and then collecting the animal's serum. Two commercially available formulations are antithymocyte globulin (Atgam), which is horse-based, and Thymoglobulin, which is rabbit-based. The antibodies produced in this manner are directed against a variety of targets on the surface of B and T cells and induce complement-mediated lymphocytolysis. The recommended doses of Atgam and Thymoglobulin are 15 mg/kg/d and 1.5 mg/kg/d, respectively, for a total of 7 to 10 days. Adequate lymphocyte depletion can be ensured by quantifying the CD2-positive lymphocytes, a marker present on all lymphocytes. Similar to OKT3, immunity may develop to the animal component of these antibodies, rendering them ineffective if further courses of therapy are necessary. An increased incidence of PTLD, lymphoma, and opportunistic viral infections has also been observed. Patients receiving either formulation are often prophylactically treated with ganciclovir to prevent CMV infection.
3. **IL-2 receptor blockers** are competitive fully humanized monoclonal anti-CD25 antibodies. CD25 antigen is the IL-2 receptor and is only present on the cell surface of activated T lymphocytes. In contrast to OKT3, there is no initial receptor agonist phase and no cytokine release syndrome.

For the two commercially available IL-2 receptor blockers, basiliximab (Simulect) and daclizumab (Zenapax), there are data to support the use of daclizumab only for induction therapy after cardiac transplantation, particularly in patients with preexisting renal dysfunction in whom calcineurin inhibitor avoidance is preferable in the early postoperative period. Fewer patients treated with daclizumab, in addition to standard triple immunosuppressant therapy, developed acute rejection compared with controls (9). Patients treated with daclizumab also had a lower severity and frequency of acute rejection during the first 3 months and had a longer time to the first episode of rejection. In contrast to other agents used for induction therapy, daclizumab does not appear to increase the risk of lymphoma, PTLD, or opportunistic viral infections. The serum half-life of daclizumab is 21 days, and dosing strategies call for a dose of 1 mg/kg every 1 to 2 weeks after transplantation, for a total of five doses (including the initial dose). There is no indication for either basiliximab or daclizumab as therapy for steroid-resistant persistent acute rejection. Given the virtual absence of side effects from IL-2 receptor blockade, the critical issue that needs to be addressed for these agents to become widely used clinically is whether the reduction in early acute rejection episodes translates into improved long-term survival and a reduction in transplant coronary vasculopathy.

- IX. **REJECTION.** In the ISHLT registry, 30% of the cardiac allograft recipients between January 2003 and June 2008 experienced rejection during the first year. Females and young patients were at higher risk than males and older patients, respectively. Allograft rejection involves both the cellular and humoral arms of the adaptive response. An ideal immune monitoring strategy has been described as the one that would be noninvasive,

TABLE 13.8 Grading Scale (2004) for Endomyocardial Biopsies

Grade	Severity of cellular rejection	Histologic findings
1R ^a	Mild	Interstitial and/or perivascular infiltrate with up to 1 focus of necrosis
2R	Moderate	≥2 foci of infiltrate with associated necrosis
3R	Severe	Diffuse infiltrate with multifocal necrosis ± edema ± hemorrhage ± vasculitis

^aR = revised.

would reliably distinguish between the presence and absence of rejection, and would detect overimmunosuppression (10). Such a strategy does not, however, exist. The immunologic status of a transplant recipient is currently monitored by immunosuppressant drug levels, echocardiographic assessment of allograft function, and EMB. Noninvasive monitoring therapies have been tested in the hope of overcoming these limitations. Gene expression profiling (GEP) test, which is also known as the AlloMap test, and cardiac magnetic resonance (CMR) imaging are examples of promising alternatives that are being evaluated.

A. Endomyocardial biopsy. The current gold standard of rejection surveillance after cardiac transplantation is EMB. However, EMB is invasive, inconvenient, expensive, and subject to sampling error and interobserver variability. Rejection of the cardiac allograft is usually clinically silent unless it is accompanied by significant hemodynamic compromise (i.e., congestive heart failure). As a result, EMBs are routinely performed for rejection surveillance (see Chapter 63). To mitigate the interobserver variability, the ISHLT revised and simplified the grading criteria for acute cellular rejection (Table 13.8) (11). Because the likelihood of acute rejection is highest early after transplantation, the frequency of biopsies is high during this period and then gradually tapers off, depending on the results (Table 13.9).

B. Surrogate markers of rejection

- 1. Peripheral biomarkers.** While high levels of circulating pretransplant, donor-specific antibodies to HLAs have been demonstrated to predict greater risk of severe

TABLE 13.9 Endomyocardial Biopsy Schedule

Weeks after transplantation	Biopsy frequency
1–4	Weekly
5–12	Every 2 wk
13–24	Monthly
25–52	Every 2 mo
Year 2	Every 3–4 mo
Years 3–4	Every 6 mo
>4 y	Only if clinically indicated
After biopsy with acute rejection	2 wk after initial biopsy

rejection, no peripheral markers have been shown to reliably correlate with allograft rejection posttransplantation among those evaluated, including cytokine levels, markers of myocardial necrosis (CK-MB and troponin), complement fragments, prothrombin, P-selectin fragments, CD69 membrane protein, soluble CD30, endothelin, serum nitrate, thromboxane A_2 , matrix metalloproteinase-1 in brain, vascular endothelial growth factor, natriuretic peptide, and C-reactive protein (12).

2. **Echocardiography.** Echocardiography is ubiquitous in cardiac transplant centers, drawing investigative attention to it as a noninvasive surveillance alternative to EMB for cardiac allograft rejection. For it to be a useful screening tool, however, echocardiography must identify graft rejection before global LV systolic dysfunction ensues. The challenge has been to identify such sentinel markers. Myocardial performance index, pressure halftime, intraventricular relaxation time, and acoustic quantification of cardiac filling volumes have not shown consistency. Changes $> 10\%$ in serial measurements of pulsed wave tissue Doppler measurements of early diastolic basal posterior wall motion velocity were able to exclude clinically relevant rejection with positive predictive value and negative predictive value of 92% and 95%, respectively. Technical limitations with this technique in the cardiac transplant population together with inconsistent observer interpretation have meant that echocardiography is neither sufficiently sensitive nor specific to supplant routine EMB (12).
3. **Gene expression profiling.** GEP is a new modality for surveillance of cardiac allograft rejection. **This test uses microarray and quantitative polymerase chain reaction (PCR) of peripheral blood mononuclear cells to measure the expression of 20 genes** (11 informative, 9 control and normalization) (13). A score ranging from 0 to 40 is generated by a multigene algorithm. It has been shown to correlate strongly with histologically diagnosed cellular allograft rejection. In the Cardiac Allograft Rejection Gene Expression Observational (CARGO) study, scores of < 34 were associated with a negative predictive value of $> 99\%$ for grade $\geq 3A/2R$ rejection. Several factors influence AlloMap score, including time posttransplantation, peripheral alloimmune activity, corticosteroid dose, and CMV. Transplant vasculopathy has been shown to be associated with increased AlloMap GEP score. GEP testing can be used in clinically stable cardiac transplant recipients who are > 15 years of age and 6 months or more posttransplantation. It is used to identify patients at low risk for moderate/severe ($\geq 3A$ original ISHLT grade or $\geq 2R$ revised ISHLT grade) cellular rejection (8). In the Invasive Monitoring Attenuation through Gene Expression (IMAGE) trial, 602 patients who had undergone cardiac transplantation at least 6 months previously were randomly assigned to the AlloMap test or EMB. The composite primary outcome of the study was allograft dysfunction, death, or retransplantation. At 2 years, the cumulative rate of this composite end point was 14.5% with GEP and 15.3% with EMB. The AlloMap test was thus not inferior to EMB in detecting allograft rejection. However, wholesale embrace of the IMAGE trial is tempered by the limitations of the trial, including the enrolment of only 20% of potentially eligible patients and of patients at lower risk for rejection. The noninferiority margin chosen was wide and included events that would not be associated with rejection since not all cases of graft dysfunction, death, or retransplantation are due to rejection (14).

The frequency of rejection surveillance using the GEP or AlloMap testing should be individualized to the patient's rejection history, immunosuppression regimen, time posttransplantation, and transplant center protocol. GEP is a cost-effective and less expensive alternative to EMB for monitoring allograft rejection in cardiac transplant patients. It has demonstrated great clinical promise in these early studies and may one day surpass EMB as the gold standard for rejection surveillance after cardiac transplantation.

4. **Cardiac magnetic resonance.** CMR is able to evaluate both the myocardial tissue composition, including edema and necrosis, and the allograft function, which makes it an attractive modality for assessing cardiac allograft rejection. Studies to date have, however, not demonstrated consistent results in human populations (15). Marie et al. (16) demonstrated a 97% negative predictive value and a 35% positive predictive value of elevated T2 relaxation times in a series of 123 scans in 68 heart transplant recipients, 82% of whom were within 1 year of transplantation. Relaxation time of at least 56 milliseconds measured with a black-blood sequence predicted moderate or greater biopsy-proven rejection with 89% sensitivity and 70% specificity, and treatment of rejection episodes resulted in normalized relaxation times. Subgroup analysis showed a correlation between positive results in conjunction with a negative biopsy and subsequent rejection episodes in the following 3 months (16). In another study, Taylor et al. (17) compared the performance of CMR with EMB in assessing acute cardiac allograft rejection in 50 patients, 802 ± 224 days posttransplantation. Acute rejection was confirmed by EMB in 11 cases and presumed in 8 cases with a recent fall in left ventricular ejection fraction (LVEF) not attributable to coronary allograft vasculopathy. CMR evaluated myocardial function, edema, and early and late post-gadolinium-DTPA contrast enhancement. With rejection defined as increased early contrast enhancement or myocardial edema, the sensitivity and specificity of CMR compared with EMB were 100% and 73%, respectively. Eight patients with presumed rejection had significantly elevated early myocardial contrast enhancement compared with controls, which reduced along with improvement in LVEF following increased immunosuppression. The drawback of CMR, however, is that it is expensive, time consuming, nonspecific, and not universally available. Moreover, it cannot be used in claustrophobic patients or those with significantly reduced renal function (i.e., those with acute kidney injury or chronic kidney disease with a glomerular filtration rate < 30 mL/min/1.73m²) in whom the use of gadolinium has the attendant risk of nephrogenic systemic fibrosis.

A. Types of rejection

1. **Hyperacute rejection** is usually fatal and is the result of allograft rejection by preformed antibodies. It can occur immediately on surgical reperfusion. The incidence of hyperacute rejection is thankfully rare in the era of PRAs and prospective crossmatches.
2. **Cell-mediated rejection** is characterized by infiltration of mononuclear inflammatory cells that are predominantly T cells directed against the allograft. Variability in the interpretation of histologic grading of cellular rejection of EMB by pathologists led to the revision of the grading system in 2004 (11). Biopsy grades of $\geq 2R$ warrant accentuation of immunosuppression. If there is no hemodynamic compromise, then patients are routinely treated as outpatients with 100 mg of prednisone taken orally for 3 days. If there is a hemodynamic compromise or persistent or recurrent severe rejection (at least grade 2R), then many therapeutic options are available, including 1 g of intravenous Solu-Medrol for 3 days, conversion from cyclosporine to tacrolimus, OKT3, Atgam, Thymoglobulin, plasmapheresis, photopheresis, and total lymphoid irradiation (4).

Grade 0R: no acute cellular rejection.

Grade 1R: mild, low-grade, acute cellular rejection.

Interstitial and/or perivascular infiltrate with up to 1 focus of myocyte damage.

Grade 2R: Moderate, intermediate-grade, acute cellular rejection.

Two or more foci of infiltrate with associated myocyte damage.

Grade 3R: Severe, high-grade, acute cellular rejection.

Diffuse infiltrate with multifocal myocyte damage \pm edema \pm hemorrhage \pm vasculitis.

3. **Antibody-mediated rejection (AMR)** occurs due to preformed or de novo alloantibody (immunoglobulin G or M) against donor antigens. Such antibodies and complements are deposited in the donor coronary microvasculature and are demonstrable by immunofluorescence or by immunohistochemistry staining against CD68, C4d, or C3d complement fragments that mediate vascular injury and, ultimately, allograft failure. There has, however, been no consensus on its diagnosis. The ISHLT has recently proposed a framework for reporting AMR (18):

pAMR 0: negative for pathologic AMR.

Both histologic and immunopathologic studies are negative.

pAMR 1 (H+): histopathologic AMR alone.

Histologic findings are present and immunopathologic findings are negative.

pAMR1 (I+): immunopathologic AMR alone.

Histologic findings are negative and immunopathologic findings are positive.

pAMR 2: pathologic AMR.

Both histologic and immunopathologic findings are present.

pAMR 3: severe pathologic AMR.

This category recognizes the rare cases of severe AMR with histopathologic findings of interstitial hemorrhage, capillary fragmentation, mixed inflammatory infiltrates, endothelial cell pyknosis and/or karyorrhexis, and marked edema. The reported experience of the group was that these cases are associated with profound allograft dysfunction and poor clinical outcomes.

AMR is not routinely screened for in EMBs unless suspected clinically because of allograft dysfunction or hemodynamic compromise. Treatment options for patients with vascular rejection include intravenous or oral steroids, plasmapheresis, or immunoadsorption (4).

- X. INFECTIOUS DISEASE AFTER TRANSPLANTATION.** The risk of infection is highest in the first year post cardiac transplantation, accounting for 29% of deaths. Thereafter, the risk falls but remains > 10%. In the first month post transplantation, nosocomial infections predominate. The therapeutic immunosuppression consequent upon transplantation leaves cardiac allograft recipients vulnerable to opportunistic infections or reactivation of latent infection, particularly between 1 and 6 months. Infections after 6 months are usually community-acquired. An infectious disease specialist with an interest in transplantation is an invaluable resource to any transplant program. The two pathogens of particular interest in the transplant patient are CMV and pneumocystis jiroveci pneumonia (PJP), formerly called pneumocystis carinii pneumonia, but there are several potential pathogens including *Mycobacterium*, *Nocardia*, *Listeria*, *Candida*, *Aspergillus*, and *Strongyloides* (1,4).

- A. Cytomegalovirus.** Primary CMV infection occurs when a CMV-negative recipient receives a CMV-positive donor organ or is infected de novo from another source. Secondary CMV infection occurs when a CMV-positive recipient has reactivation of quiescent CMV infection with viremia after immunosuppression, particularly with induction therapy or bolus immunosuppression prescribed for a rejection episode. Active CMV disease may manifest as fevers, myalgias, gastritis, colitis, pneumonitis, retinitis, or leukopenia and thrombocytopenia. The most sensitive and specific test for diagnosing CMV is quantitative PCR. PCR detects CMV DNA in plasma and quantifies the CMV viral load. Although CMV DNA replication may be detected by PCR, most patients do not have the clinical syndrome of CMV disease. The issues of whether a detectable CMV viral load will progress to the clinical syndrome and whether to treat patients with CMV detection in the absence of symptoms remain controversial.

Prophylaxis against CMV disease is considered to be the standard of care for CMV-positive recipients (regardless of the CMV status of the donor) and CMV-negative patients with a CMV-positive donor. There is no consensus on the duration

of ganciclovir therapy in these patients. Most patients are initially treated with intravenous ganciclovir, followed by a variable course of oral valganciclovir or acyclovir. Periodic monitoring of the CMV viral load may assist in guiding the duration of therapy in these patients.

Passive immunization with CMV immunoglobulin (CytoGam) may be considered in patients deemed at risk for CMV disease, particularly if they have low levels of serum immunoglobulins (< 500 mg/dL). Patients undergoing induction therapy, polyclonal or monoclonal antibody therapy for steroid-resistant rejection, or increased immunosuppressive therapy for acute rejection should be deemed at risk for reactivation of CMV disease.

The duration of therapy with valganciclovir for active CMV disease is usually 3 to 6 weeks. An undetectable CMV viral load should be demonstrated in such patients before consideration is given for antiviral therapy discontinuation (4).

- B. *Pneumocystis jiroveci* pneumonia.** Transplant recipients are at increased risk for the development of PJP because of their immunocompromised state. PJP is rare if appropriate prophylaxis with trimethoprim-sulfamethoxazole (TMP-SMX) is provided. Patients intolerant to TMP-SMX may be treated with inhaled pentamidine or dapsone. PJP is rarely seen at maintenance immunosuppressant doses in transplant patients. TMP-SMX may be discontinued at 6 to 12 months after transplantation in most patients (4).

XI. CARDIAC ALLOGRAFT VASCULOPATHY (CAV). CAV is a progressive, neointimal proliferative process in the epicardial coronary vasculature and in the microcirculation. It is common, with an incidence of 20%, 30%, and $> 50\%$ at 3, 5, and 10 years after transplantation. CAV is a significant cause of mortality beyond the first year after transplantation, accounting for 30% to 50% of deaths at 5 years. The pathophysiology of CAV is not completely understood. **Initially CAV was thought to be an accelerated form of atherosclerosis; however, it is now clear that both immunologic and nonimmunologic factors are involved in the process.** Chronic, subclinical, and immune-mediated injury at the level of the donor coronary endothelium creates a chronic inflammatory milieu. The exact mediator of the endothelial injury remains controversial, but it is probably multifactorial, including chronic humoral and cellular rejection, ischemic and reperfusion injury at the time of transplantation, and chronic CMV infection of endothelial cells. Table 13.10 lists risk factors for the development of CAV, of which older donor age and hyperlipidemia are well-established risk factors, whereas the others are potential risk factors.

Because donor hearts are denervated at explantation, **the transplant recipient typically will not experience cardiac angina from advanced CAV.** The clinical presentation of CAV previously unrecognized in a patient may include symptomatic or asymptomatic LV dysfunction, myocardial infarction, or cardiac arrhythmia, including ventricular arrhythmias, heart block, syncope, or sudden cardiac death. Owing to the usually asymptomatic nature of CAV, transplant recipients require frequent surveillance studies to detect significant vasculopathy, including coronary angiography with or without IVUS, cardiac perfusion magnetic resonance imaging, and dobutamine echocardiography. The frequency and method of surveillance are center-specific. Although coronary angiography is useful for the diagnosis of nontransplant coronary artery disease, its sensitivity is considerably less in CAV because of the diffuse nature of this disease. Coronary IVUS imaging provides useful tomographic perspective to study the development and progression of CAV and is now considered by many to be the gold standard modality for diagnosing CAV. However, not all centers have access to routine IVUS imaging and thus its use will vary greatly from center to center. The nomenclature of CAV has not been standardized until recently (19). The recommended nomenclature for CAV is as follows:

CAV0 (not significant): no detectable angiographic lesion.

ISHLT CAV1 (mild): angiographic left main (LM) $< 50\%$, primary vessel with maximum lesion of $< 70\%$, or any branch stenosis $< 70\%$ (including diffuse narrowing) without allograft dysfunction.

TABLE 13.10 Risk Factors for the Development of Cardiac Allograft Vasculopathy

Older donor age
Hyperlipidemia
Donor brain death secondary to spontaneous intracranial hemorrhage
Cytomegalovirus infection
Increased C-reactive protein levels (> 1.66 mg/L)
Recurrent cellular rejection
Humoral (vascular) rejection
HLA antigen mismatch
Donor hepatitis B and C
Female donor
Peritransplant myocardial ischemia
Pretransplant coronary atherosclerotic disease
Conventional atherosclerosis risk factors (diabetes, hypertension, and smoking)

HLA, human leukocyte antigen.

ISHLT CAV2 (moderate): angiographic LM $< 50\%$, a single primary vessel $\geq 70\%$, or isolated branch stenosis $\geq 70\%$ in branches of two systems, without allograft dysfunction.

ISHLT CAV3 (severe): angiographic LM $\geq 50\%$, two or more primary vessels $\geq 70\%$ stenosis, or isolated branch stenosis $\geq 70\%$ in all three systems; or ISHLT CAV1 or CAV2 with allograft dysfunction (defined as LVEF $\leq 45\%$ usually in the presence of regional wall motion abnormalities) or evidence of significant restrictive physiology (which is common but not specific).

Definitions

(a) A “primary vessel” denotes the proximal and middle 33% of the left anterior descending artery, the left circumflex, the ramus, and the dominant or codominant right coronary artery with the posterior descending and posterolateral branches.

(b) A “secondary branch vessel” includes the distal 33% of the primary vessels or any segment within a large septal perforator, diagonals and obtuse marginal branches, or any portion of a nondominant right coronary artery.

(c) Restrictive cardiac allograft physiology is defined as symptomatic heart failure with echocardiographic E to A velocity ratio > 2 (> 1.5 in children), shortened isovolumetric relaxation time (< 60 milliseconds), shortened deceleration time (< 150 milliseconds), or restrictive hemodynamic values (right atrial pressure > 12 mm Hg, pulmonary capillary wedge pressure > 25 mm Hg, and cardiac index < 2 L/min/m²).

The detection of significant CAV should prompt aggressive percutaneous or more rarely surgical revascularization. Because of its relationship with chronic rejection, advancement of the immunosuppressant regimen has also been advocated. Statins have been shown prospectively to decrease the incidence of transplant vasculopathy and improve survival, regardless of the patient’s lipid profile (20). Preliminary studies investigating the antiproliferative effects of TOR inhibitors (sirolimus and everolimus) suggest a significant reduction in coronary neointimal proliferation and, therefore, transplant coronary vasculopathy. In the future, the development of transplant vasculopathy may prompt a switch to a TOR inhibitor–based immunosuppressant regimen if the initial suggestion of attenuation of progression, and perhaps regression, of transplant vasculopathy is confirmed in larger, prospective clinical trials. In severe, advanced CAV, frequently the only viable option is repeat transplantation (1,4).

XII. MALIGNANCY

A. Malignancy is a common and devastating complication of cardiac transplantation. In immunocompetent people, the cellular arm of the immune system actively defends against a variety of neoplastic processes. With the initiation of immunosuppression after transplantation, this defense mechanism is rendered feeble and previously undeclared neoplastic foci may proliferate. Because up to 38% of patients undergo cardiac transplantation for ischemic cardiomyopathy, a significant proportion of which is smoking-related, lung cancers can occur. Other common tumors include lymphomas, skin cancers, colon cancers, and breast cancers. Skin cancers are particularly common in patients on azathioprine, and they usually prompt a substitution of MMF for azathioprine. Posttransplantation malignancies are particularly common in patients who have received cytolytic or induction therapy with OKT3, Atgam, or Thymoglobulin, and the risk correlates with cumulative dosing of immunosuppression. The risk of developing a malignancy as a result of immunosuppression is enhanced by the inability to adequately assess for overimmunosuppression. Underimmunosuppression is readily detected because of the development of acute rejection, whereas there is no clinical finding to suggest overimmunosuppression.

PTLD is an Epstein-Barr virus-related clonal expansion of B lymphocytes. PTLT may develop in any location but most commonly affects the gastrointestinal tract, lungs, and central nervous system. The primary treatment for PTLT is a reduction in immunosuppression (by about 50%), which can frequently be curative. Surgical debulking, systemic chemotherapy, and antiviral therapy may also be indicated in selected patients (1,4).

XIII. HYPERTENSION. Arterial hypertension commonly develops after cardiac transplantation secondary to the untoward effects of immunosuppression. **Hypertension developing after cardiac transplantation occurs in most cyclosporine-treated and tacrolimus-treated patients.** Three mechanisms proposed are as follows:

- (1) direct sympathetic activation,
- (2) increased responsiveness to direct circulating neurohormones, and
- (3) direct vascular effects.

A common end point of these proposed mechanisms is vasoconstriction of the renal vasculature, leading to sodium retention and an elevated plasma volume. Corticosteroids play a minor role in the pathogenesis of cardiac transplant hypertension, which is described as a salt-sensitive type. Abnormal cardiorenal reflexes secondary to cardiac denervation may also contribute to salt-sensitive hypertension and fluid retention.

Patients with blood pressure consistently > 140/90 mm Hg should be treated. Titrated monotherapy with either ACE inhibitors or calcium channel blockers is usually effective in about 50% of the patients. Some patients will be prone to hyperkalemia secondary to the combined effect of cyclosporine and ACE inhibition on the kidney. The use of diltiazem, verapamil, or amlodipine necessitates the use of lower doses of cyclosporine and initially more frequent cyclosporine level monitoring because these drugs are competitive antagonists of cyclosporine at the cytochrome P450 level. Combination therapy with both an ACE inhibitor and a calcium channel blocker is a commonly employed strategy. Problematic hypertensives requiring multiple agents often require diuretics as part of their regimen. Hypertension in some patients is inadequately controlled despite maximally tolerated doses of both calcium channel blockers and ACE inhibitors. The final tier of management would be to add a β -blocker such as clonidine or doxazosin in refractory cases. β -Blockers traditionally have been avoided due to their known tendency to reduce exercise performance and because of concerns about excessive bradycardia. Some transplant cardiologists, however, routinely use β -blockers to manage hypertension in their transplant patients. Thus, β -blockers are not contraindicated but rather may be used with due caution (1,4).

XIV. OUTCOMES AFTER CARDIAC TRANSPLANTATION. Survival outcomes after cardiac transplantation continue to improve on a yearly basis despite what is generally accepted as a population of transplant recipients at greater risk, primarily because of advancing recipient age and increasing severity of heart failure. The 1-year survival rate after cardiac transplantation is 84% nationwide, but it is frequently > 90% at large transplant centers. The mortality in the first year after transplantation primarily results from postoperative complications, including multiorgan failure, primary graft failure, and systemic infection. Those surviving the first year posttransplantation have a median survival of 13 years. It is unlikely that any major improvements in early posttransplant survival will occur in light of these excellent results. However, a 10-year survival rate after cardiac transplantation is only 50%. Mortality in the long term primarily results from transplant coronary vasculopathy, malignancy, and renal failure. It is hoped that a major impact can be made on long-term survival with newer immunosuppressive drug regimens that may be less nephrotoxic and more effective at preventing transplant coronary vasculopathy (1).

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RELEVANT WEB SITES

International Society for Heart and Lung Transplantation (ISHLT) (www.isHLT.org).
Scientific registry of solid-organ transplant recipients in the United States (www.ustransplants.org).

Pulmonary Hypertension

I. INTRODUCTION. Pulmonary hypertension (PH) is a routinely made diagnosis in contemporary cardiology and pulmonary clinics. It is essential for the specialist as well as the internist to have a high index of clinical suspicion for this devastating disease, as early diagnosis and referral may affect the survival. Substantial advances are being made in the management of pulmonary arterial hypertension (PAH), which is more rapidly available at centers specializing in PH.

A. Terminology/definitions. PH is defined as mean pulmonary artery pressure (mPAP) > 25 mm Hg. PH encompasses a heterogeneous group of diseases with a common clinical manifestation. The terms PH, which is a hemodynamic and pathophysiologic condition, and PAH, a clinical condition, are different terminologies that should not be used interchangeably. The clinical classification of PH is based on hemodynamic data derived from right heart catheterization (RHC). Some terminologies that are commonly employed in PH include the following:

1. **Trans-pulmonary gradient (TPG)** is defined as the pressure difference between mean left atrial pressure (LAP) (more commonly pulmonary capillary wedge pressure [PCWP] is used as a surrogate) and mPAP.
2. **Pulmonary vascular resistance (PVR)** is defined as TPG divided by the cardiac output ($PVR = TPG/CO$ in Wood units).
3. **PAH** is hemodynamically defined as PH (i.e., $mPAP \geq 25$ mm Hg) with increased PVR (more than 3 Wood units) and normal wedge pressure (< 15 mm Hg). It is a clinical condition characterized by precapillary PH and pathologic changes in the lung microcirculation.
4. **Pulmonary venous hypertension is characterized by $mPAP \geq 25$ mm Hg, $PVR > 3$ Wood unit, and elevated wedge pressure ($PCWP \geq 15$ mm Hg).**

B. Classification. The World Health Organization has endorsed the clinical classification of PH based upon pathologic, pathophysiologic, and therapeutic characteristics. The most recent classification derived from the world symposium on PH held in Dana Point, California, in 2008 is listed in Table 14.1.

C. Epidemiology. The total PH burden of the disease is substantial as it represents an end stage of multiple disease processes such as left-sided heart disease, chronic lung diseases, as well as PAH which is very rare. Most of the patients who are diagnosed with PH on routine testing (echocardiogram with pulmonary arterial systolic pressure [PASP] > 40 mm Hg) will end up having left heart disease (nearly 80%), some with lung disease and hypoxia (10%), and only a small minority (4%) will have PAH.

Data from registries estimate the prevalence at around 15 to 50 cases/million adults and its incidence at around 2.4 cases/million adults/year. Idiopathic PAH (IPAH) and familial PAH (previously known as “primary PH”) are rare diseases with a prevalence of around 6 cases/million. **Familial cases account for 5% to 10% of all PAH cases. Mutations in the bone morphogenetic protein receptor-II (BMPR2)**

TABLE 14.1 Dana Point Classification of Pulmonary Hypertension (Simplified)

Type	Subtype
1 Pulmonary arterial hypertension	Idiopathic Heritable Drugs and toxins induced Associated with CTD, HIV, portal hypertension, congenital heart disease, schistosomiasis, and chronic hemolytic anemia Persistent PH of newborn
1' Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis	
2 PH due to left heart disease	Systolic Diastolic Valvular
3 PH due to lung disease and/or hypoxia	COPD ILD Mixed obstructive and restrictive lung disease Sleep-disordered breathing Alveolar hypoventilation syndromes, etc.
4 Chronic thromboembolic PH	
5 PH with unclear and/or multifactorial mechanisms	Hematologic Systemic such as sarcoid and vasculitis

PH, pulmonary hypertension; CTD, connective tissue disease; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; ILD, interstitial lung disease.

gene have been identified in about 70% of patients with familial PAH and 10% to 40% of patients with sporadic IPAH. Hence, relatives of patients with familial IPAH should be advised about the availability of genetic testing and counseling in addition to echocardiographic screening.

PAH has been associated with environmental factors such as the use of drugs and toxins. **Anorexigens** (appetite suppressant drugs that increase serotonin release and block serotonin reuptake) have been associated with PAH, with agents such as aminorex fumarate and (dex) fenfluramine. Select patient populations at an increased risk of developing PAH are discussed below.

1. **Patients with connective tissue diseases** (CTDs), especially the **limited cutaneous form of systemic sclerosis (formerly referred to as the CREST syndrome)**. The prevalence of hemodynamically proven PAH in systemic sclerosis is around 10%. In other CTDs, such as systemic lupus erythematosus, mixed CTD, rheumatoid arthritis, dermatomyositis, and Sjögren's syndrome, PAH is observed less frequently.
2. **Human immunodeficiency virus (HIV) infection** is associated with approximately 0.5% incidence of PAH. However, because of this low incidence, routine screening is not recommended.
3. Patients with **cirrhosis and portal hypertension** are at an increased incidence of PH (5% of patients were referred for liver transplantation).

4. **Congenital heart disease** may lead to PAH when the underlying systemic-to-pulmonary shunt is not corrected. Most commonly, it occurs with conditions where blood flow is high and the pulmonary vasculature is exposed to systemic level pressures (e.g., ventricular septal defect and patent ductus arteriosus). However, high blood flow alone, as in atrial septal defect, may be sufficient. Once PVR approaches or exceeds the systemic vascular resistance, the shunt is reversed, leading to desaturation and cyanosis (Eisenmenger syndrome).

II. SIGNS AND SYMPTOMS

- A. **Symptoms.** The symptoms of PH are nonspecific and are gradual in onset; therefore, there is a lag time of about 2 years (from symptom onset to diagnosis) in 90% of patients with PAH. These symptoms may include dyspnea on exertion, fatigue, weakness, chest pain, palpitations, syncope, abdominal distention, and pedal edema. Symptoms at rest occur only at late stages of the disease and portend poor prognosis.

Some patient populations are at an increased risk for developing PH and should be carefully screened by clinicians by careful history taking, examination, and laboratory tests. These populations include patients with known, or relatives of those with, BMPR2 mutations, CTD, HIV infection, portal hypertension, prior appetite suppressant use, congenital heart disease with shunt, recent acute pulmonary embolism, left heart disease, chronic obstructive pulmonary disease, interstitial lung disease, or sleep apnea.

It is advisable to perform annual screening with echocardiography in select high-risk groups, such as

- (1) those with known BMPR2 mutation;
 - (2) first-degree relative of the patient with BMPR2 mutation or within pedigree of two or more patients with PAH;
 - (3) those with systemic sclerosis; and
 - (4) those with sickle cell disease.
- B. **Physical examination.** Physical examination may provide clues as to the cause of PH. Findings of telangiectasia, digital ulceration, and sclerodactyly suggest scleroderma, while inspiratory crackles may point toward interstitial lung disease. Patients should be carefully screened for the presence of stigmata of liver disease, such as spider naevi, testicular atrophy, and palmar erythema. The presence of clubbing suggests congenital heart disease or pulmonary veno-occlusive disease. Cardiovascular examination of patients with PH may reveal a left parasternal lift, a loud P_2 at the apex, a pansystolic murmur of tricuspid regurgitation that increases with inspiration, a diastolic murmur of pulmonary insufficiency, and a right ventricular (RV) S_3 . Lung sounds are usually normal (except for those with class 3 PH). Jugular vein distension, hepatomegaly with a pulsatile liver, peripheral edema, and ascites are ominous signs suggestive of advanced stages with right-sided heart failure.

III. LABORATORY EVALUATION

A. Blood work

1. Routine biochemistry, hematology, and thyroid function tests.
2. **Serologic testing** is important to detect the underlying CTDs, HIV (mandatory screening), thrombophilia (in chronic thromboembolic pulmonary hypertension [CTEPH]), and hepatitis (in patients with suspected liver disease). More than a third of patients with IPAH have low-titer elevation in antinuclear antibodies. Systemic sclerosis is the most important CTD to exclude because of high prevalence of PAH in this syndrome. Anti-centromere antibodies are usually positive in limited scleroderma as are other antinuclear antibodies, including dsDNA, anti-Ro, U3-RNP, B23, Th/To, and U1-RNP. In the diffuse variety of scleroderma, U3-RNP is positive. In patients with systemic lupus erythematosus, anticardiolipin antibodies may be found.

3. **Biomarkers.** Several circulating biomarkers have prognostic implications in patients with PAH, but their value in everyday clinical practice is still not established. Uric acid levels are shown to be increased in patients with IPAH, and elevated plasma troponin T levels (> 150 pg/mg) have been associated with worse outcomes in patients with CTEPH and PAH. BNP levels have also been used to monitor response to therapy or clinical course, as those with persistently elevated levels have worse outcomes. Similarly, NT-proBNP below cutoff levels $< 1,400$ pg/mL has been associated with better outcomes. BNP/NT-proBNP plasma levels should be checked for the initial risk stratification and may be considered for monitoring the effects of treatment, in view of their prognostic implications. Low and stable or decreasing BNP/NT-proBNP may be a marker of successful disease control in PAH.
- B. **The electrocardiogram (ECG).** In typical cases of PH, the ECG shows right atrial (RA) dilatation, RV hypertrophy with strain, and a right axis deviation. In advanced stages of the disease, atrial flutter or atrial fibrillation often occurs, leading to further clinical deterioration.
- C. **Chest radiograph.** Initial chest x-rays are abnormal in majority (90%) of patients with IPAH at the time of diagnosis. There is often central pulmonary arterial (PA) dilatation with “pruning” (loss) of the peripheral blood vessels, clear lung fields, and a prominent RV border. The chest x-ray may also point to lung abnormalities and show features suggestive of left heart disease.
- D. **Echocardiography.** If PH is suspected based on history, risk factor assessment, and physical examination, an echocardiogram is the next appropriate study. By using the Doppler technique, peak velocity of the tricuspid regurgitation jet can be measured. From this measured velocity, the pressure difference between right ventricle and right atrium can be estimated by employing the simplified Bernoulli equation ($\Delta P = 4v^2$). On condition that there is no pulmonic valve stenosis, $PASP = 4 \times (\text{tricuspid regurgitant jet velocity})^2 + \text{right atrial pressure (RAP)}$. RAP can be estimated on the basis of inferior vena cava (IVC) characteristics. If the IVC is plethoric and there is clinical evidence of Jugular venous distension (JVD), RAP is presumed to be 10 to 15 mm Hg, whereas if findings are normal, it is usually calculated as 5 mm Hg.
- Other echocardiographic characteristics may raise the suspicion of PH, such as RA or RV dilatation, flattening of the interventricular septum with D-shaped left ventricle, increased RV wall thickness, dilatation of the pulmonary artery, and the presence of pericardial effusion. These features tend to occur later in the course of the disease.
- Although echocardiography is a useful screening tool, Doppler-derived pressure estimation can both underestimate PASP in patients with severe tricuspid regurgitation and overestimate PASP in non-PH patients. Ultimate confirmation requires RHC.
- E. **Right heart catheterization.** RHC is required to *confirm the diagnosis of PH, to assess the etiology and severity, and to test for vasoreactivity of the pulmonary circulation*. At experienced centers, morbidity (1.1%) and mortality (0.055%) rates are low. Consecutively, RAP, right ventricular pressure (RVP), PAP, and PCWP are recorded using a balloon-tipped fluid-filled catheter (Table 14.2). Cardiac output can be determined using the thermodilution method and/or the Fick method (measurement of mixed venous saturation SvO_2 needed). The PCWP is taken as a surrogate measure of LAP and, in the absence of mitral stenosis, left ventricular end-diastolic pressure (LVEDP). This measurement is very important because it helps differentiate PH associated with left heart disease from other conditions. However, it is subject to error in measurement and interpretation. Occasionally, it may be necessary to perform a left heart catheterization for direct measurement of LVEDP.

TABLE 14.2 Normal Values of Pressures and Measurements Derived from a Right Heart Catheterization

Measured characteristic	Normal value
Right atrial pressure	Mean 1–10 mm Hg
RVSP/RVDP	15–30/1–10 mm Hg
PASP/PADP	15–30/5–10 mm Hg (mean < 20 mm Hg)
PCWP	Mean 5–12 mm Hg
LVEDP	5–12 mm Hg
Cardiac output	5–7.5 L/min
Cardiac index	2.5–4.0 L/min/m ²
PVR	0.25–1.6 Wood units
TPG	4–6 mm Hg

RVSP/RVDP, right ventricular systolic and diastolic pressures; PASP/PADP, pulmonary artery systolic and diastolic pressures; PCWP, pulmonary capillary wedge pressure; LVEDP, left ventricular end-diastolic pressure; PVR, pulmonary vascular resistance; TPG, transpulmonary gradient.

Temporal evolution of the hemodynamic variables with progression of PAH is depicted in Figure 14.1. As the disease progresses, the right ventricle starts to fail, leading to reduction in CO. As a result, PAP may decrease again. This decrease may give a false impression of hemodynamic improvement or suggest that there is mild to moderate disease. Therefore, it is imperative to measure PVR, which will be high in this situation. Usually, the RAP and PCWP also increase, implying RV failure and left ventricular (LV) diastolic dysfunction, respectively. The latter is the consequence of ventricular interdependence and abnormal compliance of the left ventricle produced by an enlarged right ventricle.

Vasoreactivity testing in PAH: In PAH, vasoreactivity testing should be performed to identify patients who may benefit from long-term therapy with calcium channel blockers

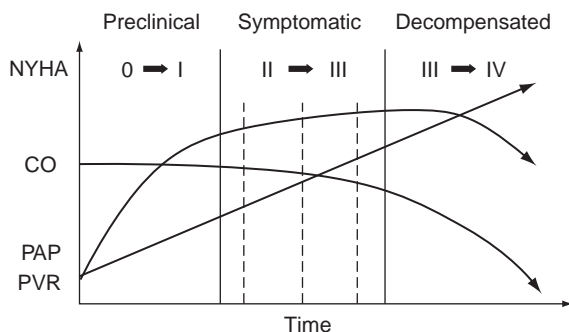


FIGURE 14.1 Evolution of hemodynamic variables in function of disease severity. CO, cardiac output; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance. (From Galie N, Manes A, Palazzi M, et al. Pharmacological impact on right ventricular remodelling in pulmonary arterial hypertension. *Eur Heart J*. 2007; 9:H68-H74, with permission.)

(CCBs). The agent most often used to test this is inhaled NO, with (i.v.) epoprostenol and (i.v.) adenosine as alternatives.

A positive acute response is defined as a > 10 mm Hg decrease in mPAP to reach an absolute value of mPAP < 40 mm Hg with an increased or unchanged CO and without significant drop in systemic blood pressure.

In patients with IPAH, about 10% to 15% are acute responders and nearly half of these will prove to be long-term responders with a more favorable prognosis. This concept is less clear in other forms of PAH, although vasoreactivity testing is still recommended but controversial in congenital heart disease. It is not useful in other forms of PH (groups 1', 2, 3, 4, and 5). In veno-occlusive disease and left heart disease, it can even provoke pulmonary edema. However, in patients considered for heart transplantation, pulmonary vasoreactivity testing may be used to assess reversibility and operability.

It is important to understand the difference between PAH vasoreactivity testing and the assessment of PH reversibility in left-sided heart failure. In PAH, vasodilator response testing is performed to select patients who may respond favorably to CCBs as the first agent versus those who will likely not. In left-sided heart failure and PH, vasodilatory drugs that affect the LV afterload, such as sodium nitroprusside, are given with an intention to reduce LV filling pressure and, evaluate for reversible pulmonary hypertension. Those who have persistent elevation in TPG and PVR to high levels (such as when TPG remains elevated to > 15 mm Hg and/or PVR is > 3 Wood units despite the reduction of PCWP to < 15 mm Hg) are at high risk for transplant failure, as the transplanted heart may not withstand persistently elevated PAPs, which results in right heart failure.

F. Pulmonary testing and arterial blood gas (ABG). Pulmonary function tests and ABGs are used to identify underlying airway or parenchymal lung disease. Patients with PAH usually have decreased lung diffusion capacity for carbon monoxide (typically in the range of 40% to 80% predicted) and mild to moderate reduction in lung volumes. Arterial oxygen partial pressure is normal or only slightly lower than normal at rest and arterial carbon dioxide partial pressure is decreased because of alveolar hyperventilation. The severity of emphysema and of interstitial lung disease can be diagnosed using high-resolution computed tomography (CT). If clinically suspected, screening overnight polysomnography may diagnose significant obstructive sleep apnea.

G. Six-minute walk distance. The 6-minute walk test (6MWT) is the most commonly employed measure of exercise capacity in patients with PH, both in clinical assessment and in research settings. In addition to the distance walked, the degree of dyspnea (Borg score) and oxygen saturation are also measured. **A 6-minute walk distance of < 332 m and a drop in oxygen saturation by > 10% are suggestive of poor prognosis.** It is also measured on routine follow-ups and can be indicative of clinical deterioration. It may also be used to assess the response to therapy.

H. Other tests. Chest CT and ventilation-perfusion (V/Q) scans are indicated to exclude primary parenchymal or thromboembolic diseases as a cause of PH. For excluding thromboembolic disease, V/Q scan is the preferred screening test. A normal or low-probability V/Q scan effectively excludes CTEPH with a sensitivity of 90% to 100% and a specificity of 94% to 100%, while a high-probability scan warrants further evaluation with a pulmonary angiogram. Pulmonary angiography may be considered at specialized centers in cases of CTEPH to determine surgical candidacy.

IV. PATHOGENESIS

A. Hemodynamically, PH is a disease state with increased pulmonary pressures.

Applying Ohm's law to the pulmonary circulation

TPG or pressure difference (mPAP – PCWP) = flow (CO) × resistance (PVR).

Thus, elevated mPAP may be a consequence of *elevation in PCWP, increase in flow, or increase in PVR*. However, pulmonary vessels are highly compliant and capable of recruitment with progressive reduction in PVR for the increment in flow. These low-pressure, low-resistance, and high-compliance characteristics of the pulmonary vascular bed are regulated by a balance between vasodilators and vasoconstrictors and between cell proliferation and apoptosis. Genetic and environmental factors may disturb this balance, resulting in excessive vasoconstriction, vascular remodeling, and micro-thrombosis, which leads to pulmonary (arterial) hypertension. This leads to elevated PVR and an increase in RV afterload, ultimately resulting in RV dilatation and hypertrophy. This may progress to RV failure with further dilatation, thinning of the wall and tricuspid regurgitation, and worsening outcome.

B. Histologically, PAH is a panvasculopathy predominantly affecting the small pulmonary arteries. The initial lesions seem to be intimal hyperplasia and medial hypertrophy followed by more irreversible lesions such as intimal fibrosis, thrombosis in situ, inflammation, and plexiform arteriopathy. These lesions may be present in various distributions, local or diffuse, in a patient.

C. Molecular and endothelial abnormalities. Various vasoactive molecules play an important role in the pathologic evolution of PAH. Our understanding of these factors and various pathologic forces is limited, but some pathways have been elucidated mainly due to their therapeutic potential (Fig. 14.2).

1. Prostacyclin/thromboxane A_2 : Prostacyclin and thromboxane A_2 are arachidonic acid metabolites in vascular cells. Prostacyclin has potent vasodilating, antiproliferative, and platelet-inhibiting properties, whereas thromboxane A_2 has the opposite effect. In PAH, the balance is shifted toward thromboxane A_2 in small and medium-sized pulmonary arteries.

2. Endothelin-1 (ET-1): ET-1 is produced by endothelial cells and exerts its effect on the smooth muscle cells through two receptors: endothelin receptor A (ET_A), expressed on vascular smooth muscle cells, and endothelin receptor B (ET_B), expressed on both vascular endothelial cells and smooth muscle cells. Stimulation of both receptors on the vascular smooth muscle cells causes vasoconstriction and has a mitogenic effect, whereas stimulation of ET_B on the endothelial cells causes vasodilatation via increased production of prostacyclin and nitric oxide (NO). In patients with PH, ET-1 levels are increased and ET-A receptors are abundant.

3. Nitric Oxide: NO is produced in endothelial and epithelial cells in the lung from L-arginine by three isoforms of NO synthases (NOSs). It is a potent vasodilator and an inhibitor of platelet activation and of vascular smooth muscle cell proliferation. Once formed, the effects of NO are mediated by cyclic guanosine monophosphate (cGMP), which is rapidly inactivated by the phosphodiesterase enzymes, especially type 5 (PDE-5). Decreased endothelial NOS (NOS 3) has been observed in patients with PAH.

4. Others: Various molecules such as serotonin, vasoactive intestinal peptide, and angiotensin-1, and various inflammatory cells have been associated with PAH.

V. TREATMENT. The treatment of group 1 PH (or PAH) is primarily in the form of pulmonary-specific vasodilator therapy, whereas treatment in groups 2, 3, and 4 PH is mainly oriented toward treating the underlying condition (such as left heart disease and chronic lung disease).

A. General measures. A few general measures apply to all the PH groups:

- (1) Mild physical activity, possibly via exercise rehabilitation, is beneficial.
- (2) Routine influenza and pneumococcal vaccinations are recommended.
- (3) Contraception should be discussed with females of child-bearing age, as pregnancy carries a 30% to 50% mortality risk and is contraindicated.

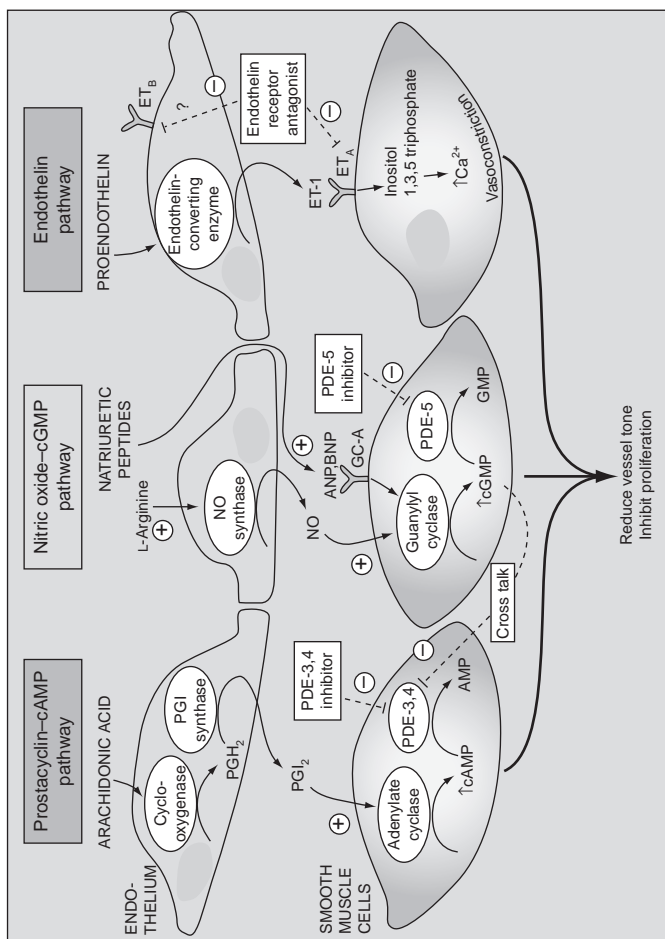


FIGURE 14.2 Therapeutic targets in pulmonary hypertension. cAMP, cyclic adenosine monophosphate; cGMP, cyclic guanosine monophosphate; PGI₂, prostacyclin; PGH₂, prostaglandin H₂; PDE, phosphodiesterase; NO, nitric oxide; ET, endothelin. (Reprinted from Benza RL, Park MH, Keogh A, et al. Management of pulmonary arterial hypertension with a focus on combination therapies. *J Heart Lung Transplant*. 2007;26(5):437–446, with permission from Elsevier.)

- (4) Oxygen supplementation is advised to maintain saturation above 90%.
- (5) Exposure to high altitude should be avoided. If flying, supplemental oxygen should be used if the patient's preflight saturation is less than 92%.
- (6) Diuretic therapy is indicated to manage RV failure with volume overload.
- (7) Digoxin may be considered in the case of atrial tachyarrhythmias.
- (8) Oral anticoagulation is recommended in CTEPH, in IPAH, and in advanced diseases (e.g., continuous i.v. therapy). In PAH, a low therapeutic value of international normalized ratio (between 1.5 and 2) is generally targeted; however, this has not been evaluated in a randomized controlled trial (RCT).

B. Pulmonary vasodilators. The initial treatment choice in PAH is guided by vasoreactivity testing. For the responders (about 10% to 15% of the IPAH population), CCBs are the first line of treatment. Careful reassessment for safety and efficacy is mandatory, because only half of these patients will prove to be long-term responders and many will need additional vasodilators. The current treatment algorithm for PAH as suggested by the 2009 ACCF/AHA expert consensus document is shown in Figure 14.3.

1. Prostacyclin analogs: Prostacyclin is a potent endogenous vasodilator and an inhibitor of platelet aggregation and also appears to have antiproliferative activity. This may explain why *epoprostenol* (Flolan) can be used to acutely lower PAPs (as used in vasoreactivity testing) as well as to achieve long-term hemodynamic improvement in patients with PH who are nonresponders. In RCTs, *epoprostenol* has been shown to improve the functional class, exercise tolerance, hemodynamics, and survival in patients with IPAH. *Epoprostenol* has to be administered in a continuous i.v. infusion, and early titration often results in unbearable side effects of nausea, headache, flushing, jaw and leg pain, and diarrhea. Adverse events related to the delivery system include pump malfunction, local site infection, catheter obstruction, and sepsis. *Treprostinil* (Remodulin) is another prostacyclin analog that can be administered by inhalation, orally, or via continuous subcutaneous pump. It has been shown to improve the exercise

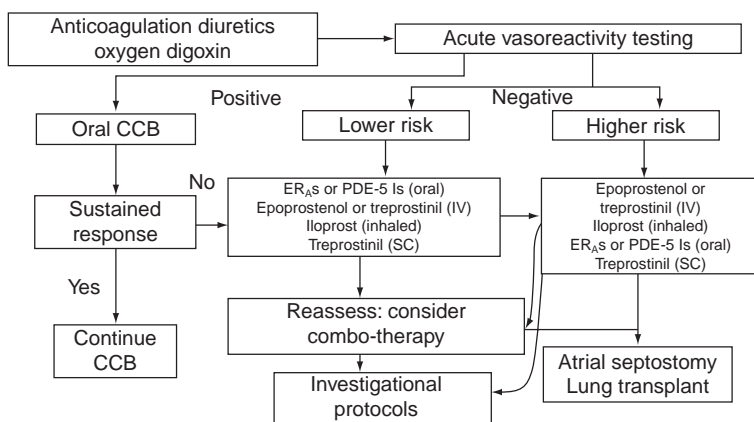


FIGURE 14.3 PAH treatment algorithm. CCB, calcium channel blocker; ERA, endothelin receptor antagonist; PDE-5 Is, phosphodiesterase type 5 inhibitors. (Reprinted from McLaughlin VV, Archer SL, Badesch DB, et al. ACCF/AHA 2009 Expert Consensus Document on Pulmonary Hypertension. *J Am Coll Cardiol.* 2009;53(17):1573–619, with permission from Elsevier.)

capacity, hemodynamics, and symptoms. Infusion site pain is the most common side effect. *Iloprost* (Ventavis) is available as an aerosol administration and has a proven beneficial effect in patients with PAH and CTEPH.

2. **Endothelin receptor antagonists (ERAs):** *Bosentan* (Tracleer) is an oral active dual ET_A/ET_B receptor antagonist that has been shown to improve the exercise capacity, functional class, hemodynamics, and cardiac performance as measured by echocardiography and clinical outcomes. *Sitaxsentan* and *ambrisentan* are more selective ET_A receptor antagonists with similar benefits as bosentan. Liver injury and teratogenicity are major concerns and require monthly monitoring.
3. **PDE-5 inhibitors:** Orally active PDE-5 inhibitors prevent the degradation of cGMP, causing vasorelaxation. *Sildenafil* (Revatio) has favorable effects on exercise capacity, symptoms, and hemodynamics. *Tadalafil* (Adcirca) has the same effects, although it also delays the time to clinical worsening. Headache, flushing, dyspepsia, and epistaxis are the usual side effects.

In low-risk patients, oral therapy with ET receptor antagonists or PDE-5 inhibitors is the first choice, whereas i.v. epoprostenol is reserved for the high-risk population. Combination therapy is being routinely employed if treatment goals are not achieved with one compound (“goal-directed therapy”). The rationale is based on attacking different pathologic processes with different agents.

- C. **Treatment of non-group 1 PAH.** Many pulmonary vasodilators have been evaluated for various non-PAH groups such as left-sided heart disease and lung disease. The following recommendations are based on current evidence:
 1. **Group 2 PH (left-sided heart disease):** prostanoids and ERAs are associated with an increased event rate in patients with LV dysfunction and are contraindicated. There is some evidence of improvement in the quality of life, exercise performance, and hemodynamics with sildenafil in patients with left heart disease and in patients bridged to transplantation with a left ventricular assist device.
 2. **Group 3 PH (lung disease or hypoxia):** pulmonary vasodilators are not recommended.
 3. **Group 4 PH (CTEPH):** prostanoids, ERAs, or PDE-5 inhibitors may be used prior to surgery to improve hemodynamics. It may be used in patients with predominant peripheral disease or in those with persistent PH after surgery.
- D. **Surgical therapies.** In CTEPH, surgery (pulmonary endarterectomy) is potentially curative in patients with accessible (proximal) disease. It is recommended that surgical evaluation and procedure be performed at high volume centers. Balloon atrial septostomy is rarely performed for palliation in patients with advanced PAH with recurrent syncope and/or right heart failure who have failed all available medical treatments. RV assist devices have emerged as a therapy in postoperative RV failure in the presence of PH. Heart–lung transplantation should be considered in a subset of eligible patients who remain in New York Heart Association functional class III or IV or in those who cannot achieve a significant exercise and hemodynamic improvement after 3 months of epoprostenol therapy.

VI. CONTROVERSIES. Several controversies exist in the clinical and research arenas regarding PH, leading to frequent difference of opinions among referring internists, pulmonologists, and cardiologists. It is therefore important to identify such areas of concern. This may help target future research and identify these patients who would benefit from management at a specialized center where a multidisciplinary approach may be provided.

- A. Most therapies (except epoprostenol) in PAH have not shown mortality benefits. Most therapeutic trials are small randomized clinical trials with soft end points such as 6MWT, exercise tolerance, and improvement in dyspnea scoring. While this raises

valid concerns regarding the long-term benefit of many expensive drugs, it is interesting that the overall survival in this patient population is improving.

- B. Pulmonary vasodilators have generally been ineffective or harmful in patients with left-sided heart failure. However, PDE-5 inhibitors are an exception, as there have been multiple small studies that suggest improvement in exercise parameters and hemodynamics. One study, Phosphodiesterase-5 Inhibition to Improve CLinical Status And EXercise Capacity in Diastolic Heart Failure Study (RELAX), is currently enrolling participants to study the effect of sildenafil in patients with diastolic heart failure.
- C. In “out-of-proportion” PH, many patients with left-sided heart failure may have only modest increase in PCWP (< 22 to 25 mm Hg) but very high PAP (systolic PAP > 60 mm Hg) with high TPG (> 18 mm Hg). This usually happens in patients who have developed a “fixed” PH, as opposed to a very few who have both left-sided heart failure and PAH.
- D. Pulmonary vasoreactivity is often used in heart transplant candidates with “out-of-proportion” PH by administering sodium nitroprusside or nitroglycerin in the cardiac catheterization laboratory and assessing hemodynamics with reduction in PCWP. Those who have reduction in PAP and TPG may be able to undergo transplantation without right heart failure.
- E. The treatment for “out-of-proportion” PH is primarily focused on treating the underlying left-sided failure.

VII. PROGNOSIS AND FOLLOW-UP

- A. **Prognosis.** Survival in patients with PH differs between PH groups and also within each group depending on the etiology. For example, the prognosis in patients with severe aortic stenosis with PH will be different from that of patients with diastolic heart failure and PH. Similarly, it is quite different between idiopathic and scleroderma-related PH. Evaluating disease severity and predicting survival is important because it may guide clinical management. Best data regarding prognosis are available for the IPAH subset population. The natural history of this group shows survival rates of 68%, 48%, and 34% after 1, 3, and 5 years, respectively. There is registry level evidence that prognosis has improved with pulmonary vasodilator therapies. Table 14.3 outlines clinical, echocardiographic, and hemodynamic features that may

TABLE 14.3 Prognostic Variables in Pulmonary Hypertension

Lower	Determinants of risk	Higher
No	Clinical evidence of RV failure	Yes
Gradual	Progression	Rapid
II, III	WHO class	IV
Longer (> 400 m)	6-Min walk distance	Shorter (< 300 m)
Minimally elevated	BNP	Very elevated
Minimal RV dysfunction	Echocardiographic findings	Pericardial effusion Significant RV dysfunction
Normal/near-normal RAP and CI	Hemodynamics	High RAP, low CI

RV, right ventricular; BNP, brain natriuretic peptide; RAP, right atrial pressure; CI, cardiac index. Adapted from McLaughlin VV, Presberg KW, Doyle RL, et al. Prognosis of pulmonary arterial hypertension*: ACCP evidence-based clinical practice guidelines *Chest*. 2004;126:78s–92s.

predict the prognosis in patients with PAH. Again, these data are mainly derived from the IPAH population, and it is unknown whether these data are transferable to other P(A)H populations.

B. Follow-up

- 1. Frequency:** Longitudinal follow-up of patients with PAH should be done at a center that specializes in PAH management with a sizeable patient population. Such centers have nurses, physicians, and ancillary support who are experienced in managing the disease and its complications. The frequency of follow-up depends on the clinical course. Those who have stable clinical course (i.e., with no evidence of heart failure, normal RV size/function, functional class I–II, 6MWT > 400 m, normal/near-normal hemodynamics, and stable BNP levels, and those maintained on oral therapy) should have clinical visits every 3 to 6 months. Unstable patients—those with sign of right heart failure, 6MWT < 300 m, abnormal hemodynamics, increasing BNP, and on i.v. therapy or combination therapy—should be evaluated every 1 to 3 months.
- 2. Routine evaluation:** Assessment at each visit should include physical examination, assessment of functional class, 6MWT at each visit, and echocardiogram at 6 to 12 months, and blood work including biomarkers are usually performed at each visit or with change in clinical status or therapy; RHC is performed every 6 to 12 months in unstable patients and in stable patients it is performed when there is clinical deterioration or change in therapy.

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SECTION



Valvular Heart Disease

EDITOR

Brian P. Griffin

Aortic Valve Disease

I. AORTIC STENOSIS

A. Introduction. Aortic stenosis (AS) causes progressive obstruction of the left ventricular outflow tract (LVOT), resulting in pressure hypertrophy of the left ventricle and the classic symptoms of heart failure, syncope, and angina pectoris. Stenosis most commonly occurs at the level of the valve (AS); however, subaortic and supravalvular stenoses are also well-defined entities. Untreated AS is associated with significant morbidity and mortality. As prompt recognition and treatment are associated with normalized life expectancy in those patients with symptomatic severe AS, careful evaluation and management can have significant impact on survival.

B. Etiology

1. Valvular AS has several causes, including congenital, rheumatic, bicuspid, and most commonly inflammation with resultant calcification.

- a.** The most common cause of AS in the United States is calcific degeneration. Although initially thought to be the result of normal “wear and tear” of the valve leaflets, there is now ample evidence that suggests that the progression of stenosis is related to an active process of inflammation involving the renin-angiotensin system, lipid accumulation, and resultant calcification. Several inflammatory pathways are implicated, including those that utilize osteopontin, bone morphogenetic proteins, and receptor activator of nuclear factor- κ B ligand.

Aortic sclerosis is caused by calcification and thickening of the aortic valve without the increased gradients as seen in AS. Both aortic sclerosis and calcific aortic stenosis have been associated with traditional risk factors for atherosclerosis, such as smoking, hypertension, and hyperlipidemia. Aortic sclerosis is associated with an increased risk of cardiovascular death and myocardial infarction and can progress to AS. Other conditions associated with calcific AS include Paget’s disease and end-stage renal disease.

- b. Bicuspid valves** are present in 1% to 2% of the population, are predominant in men, and occur in **9% of first-degree family members** of those afflicted. The most common anatomic abnormality seen in a bicuspid valve is the fusion of the right and left coronary cusps. Concurrent **coarctation, aortic root dilation, and a propensity for aortic dissection are seen** in a minority of patients. Severe stenosis typically develops by the fifth or sixth decade; however, earlier and later presentations are not uncommon. Unicuspid valves open only at one commissure, are uncommon, and are usually severely stenotic at an early age.

The most recent American College of Cardiology/American Heart Association (ACC/AHA) valve guidelines (2006) highlight the importance of evaluating the aorta and valve in bicuspid aortic valve with echocardiography or, if this is inadequate, with other imaging modalities such as magnetic resonance imaging or computed tomography. In some instances, the aorta may require surgical intervention before the valve. The guidelines recommend that patients with an aortic diameter > 4 cm and bicuspid valve should have

yearly follow-up of aorta size and should have **surgical intervention if the aorta is > 5 cm or increases by > 0.5 cm in a year**, irrespective of the valve lesion severity. **If the valve requires surgery, then aorta replacement is recommended if the aorta is > 4.5 cm at the time of surgery.** β -Blockers should be considered in bicuspid aortic valve patients in the presence of ascending aorta enlargement.

- c. **Rheumatic AS** often coexists with aortic regurgitation (AR) and mitral valve lesions. It is a rare cause of isolated severe AS in the industrialized world. Fusion of the commissures occurs leaving a small central orifice.
2. **Subvalvular AS.** This is a congenital condition, although it may not be apparent at birth. Typically, a circumferential **fibromuscular membrane involving the anterior mitral valve leaflet is present in the LVOT below the aortic valve.** In more extreme cases, a tunnel-like obstruction may be present, rather than a discrete membrane. The pathogenesis of this condition is not perfectly understood but is thought to represent a maladaptive response to abnormal flow dynamics in the LVOT. It may exist with other left-sided obstructive lesions, such as coarctation as part of Shone's syndrome. The condition may recur even after successful membrane resection. Subvalvular AS may be difficult to distinguish from hypertrophic cardiomyopathy, especially when secondary left ventricular hypertrophy (LVH) is pronounced.
3. **Supravalvular AS** is uncommon. It may occur as part of a congenital syndrome such as Williams syndrome caused by a mutation in the elastin gene (i.e., associated hypercalcemia, elfin facies, developmental delay, small stature, and multiple stenoses in the aorta and peripheral arteries) or be caused by lipid deposits in severe forms of familial hypercholesterolemia. Obstruction occurs above the valve in the ascending aorta.

C. Pathophysiology

1. **Pressure overload.** All forms of AS are characterized by progressive narrowing of the LVOT. To maintain cardiac output in the face of increased afterload, the left ventricle must generate higher systolic pressures, which increases LV wall stress. In response to the pressure overload and increased wall stress, the left ventricle undergoes compensatory, concentric hypertrophy. The increase in LV wall thickness allows the wall stress to normalize according to Laplace's law: wall stress = $(\text{pressure} \times \text{radius}) / (2 \times \text{thickness})$.
2. **Diastolic dysfunction.** LV diastolic function is determined by LV relaxation properties and LV compliance (i.e., change in volume with change in pressure [dV/dP]). Increased afterload and LVH lead to a reduction in LV compliance. Furthermore, there are changes in strain and torsion characteristics of the left ventricle in AS. Passive early diastolic filling is reduced, and maintenance of an adequate LV preload becomes more dependent on active left atrial contraction.
3. **Supply-demand mismatch.** Myocardial oxygen demand is determined by heart rate, cardiac contractility, and myocardial wall stress. Over time, LVH is unable to compensate for the increase in wall stress imposed on the left ventricle by progressive pressure overload. As the AS becomes more severe, wall stress and myocardial oxygen demand increase in parallel. Concurrently, AS is associated with a decrease in myocardial oxygen supply. Progressive LVH and diastolic dysfunction lead to an elevation in left ventricular end-diastolic pressure (LVEDP). Elevated LVEDP leads to decreased perfusion pressure across the coronary bed and causes endocardial compression of small intramyocardial arteries, impairing coronary flow reserve. The imbalance between myocardial oxygen supply and demand can precipitate ischemia during exertion.

- D. **Natural history.** The classic survival curve for patients with untreated AS, as described by Ross and Braunwald (1), is shown in Figure 15.1.

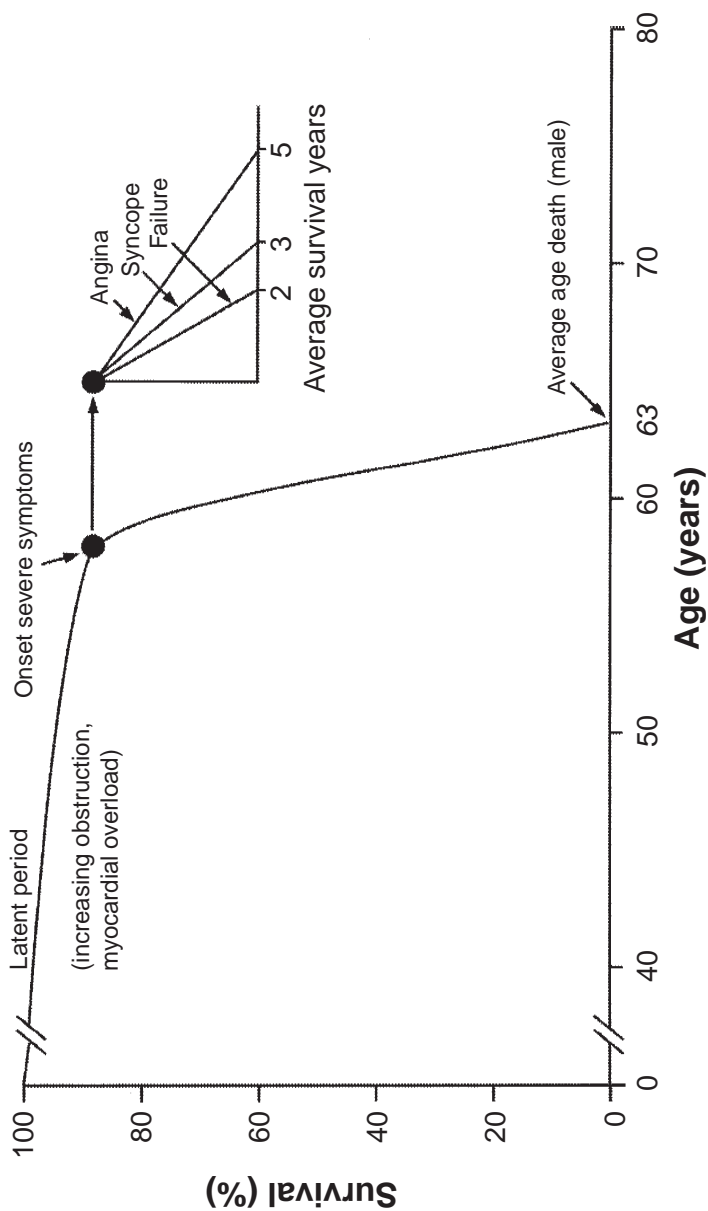


FIGURE 15.1 Patient survival in aortic stenosis.

1. Asymptomatic patients

- a. The disease process of AS is characterized by a long latent phase, during which the patient has no symptoms. This period is associated with near-normal survival. The risk of sudden cardiac death in asymptomatic patients with critical AS is $< 2\%$ per year.
- b. Although the underlying cause helps predict the age of symptom onset, there is marked individual variability in the length of the latent period and the subsequent rate of progression of disease. In general, among asymptomatic valvular AS patients, the mean aortic valve gradient rises by 7 mm Hg/y and the aortic valve area (AVA) decreases by 0.1 cm²/y.
- c. Because of the variable rate of disease progression, all patients with AS should be advised to report the onset of any symptoms to their physician and should be followed clinically and with Doppler echocardiography with increasing frequency as the lesion progresses.
- d. Once the **valve becomes severely narrow**, as evidenced by a peak **Doppler velocity of 4 m/s across it, the likelihood of developing symptoms or requiring surgical intervention over the following 2 years is very high**. This likelihood is increased if the valve is heavily calcified.

2. Symptomatic patients.

When symptoms of AS develop, the survival rate decreases markedly, unless aortic valve replacement (AVR) is performed.

- a. Patients with **angina** have a 50%, 5-year survival rate without surgical intervention. Those with **syncope** have a 50%, 3-year survival rate without surgical intervention. Patients with **heart failure** have a mean survival time of < 2 years if treated medically.
- b. In patients with severe, symptomatic AS, sudden cardiac death can occur in the setting of hypotension or arrhythmia due to ischemia, LVH, or impaired LV function.
- c. Signs and symptoms of severe AS might be subtle in some patients. Information concerning activity levels from family members may be useful in this situation, as may a symptom-limited stress echocardiogram. Exercise stress testing is absolutely contraindicated in the setting of definite symptoms.

E. Clinical manifestations

1. Signs and symptoms.

The onset of symptoms usually indicates progression to severe AS and heralds the need for surgical evaluation.

- a. **Angina.** Patients with severe AS can experience ischemia from myocardial supply-demand mismatch due to high LV diastolic pressures, decreased myocardial perfusion, and increased wall stress. Angina can also result from underlying coronary artery disease (CAD). CAD is common among patients with severe AS. It occurs in 40% to 80% of patients with angina and in 25% of patients without angina.
- b. **Syncope.** Because of fixed LVOT obstruction, patients with severe AS are unable to augment their cardiac output under conditions of low systemic vascular resistance (SVR) (i.e., induced by certain medications or vasovagal reactions). The ensuing hypotension can cause presyncope, syncope, or even cardiovascular collapse and death. Syncope can also result from atrial or ventricular arrhythmias, abnormal baroreceptor function, or abnormal vasodepressor responses induced by LV pressure overload.
- c. **Heart failure** symptoms, such as exertional dyspnea, orthopnea, or paroxysmal nocturnal dyspnea, and fatigue can result from LV systolic or diastolic dysfunction.

2. Physical findings

- a. **Arterial examination.** A hallmark finding in AS is a diminished and delayed carotid upstroke, *pulsus parvus et tardus*. However, elderly patients

with noncompliant vessels or patients with concomitant AR may often maintain a normal carotid pulsation, despite severe AS. These findings are rare with obstruction above or below the valve. It is classically thought that severe AS is not associated with hypertension, as the narrowed valve limits the flow into the arterial system and thus gives rise to a narrowed pulse pressure and relative hypotension. In fact, in the elderly, hypertension and severe AS may often coexist, likely as a result of impaired elasticity of the aortic walls, and the finding of arterial hypertension does not preclude significant associated AS.

- b. **Palpation.** With LVH and normal LV cavity dimensions, the apical impulse is usually nondisplaced, diffuse, and sustained. However, the apical impulse may later be displaced when there is LV systolic dysfunction. A double apical impulse represents a palpable a wave or S_4 , caused by a noncompliant left ventricle. A systolic thrill may be palpable in the second right intercostal space.
- c. **Auscultation.** The main auscultatory findings are shown in Figure 15.2.
 - (1) The typical murmur of AS is a systolic ejection murmur heard at the right upper sternal border that radiates to the neck. With a mobile bicuspid valve, an aortic opening sound may precede the murmur. As the severity of stenosis increases, the murmur becomes longer and peaks later in systole. The intensity of the murmur does not necessarily correspond to the severity of AS. S_1 is usually normal in AS. As the AS becomes more severe, the aortic component of S_2 diminishes and eventually disappears, resulting in a soft, single S_2 . Often, with severe AS, S_2 is paradoxically split because of the prolonged ejection duration through the severely narrowed valve. S_3 is indicative of poor LV systolic function. An S_4 is common because of reduced LV compliance.

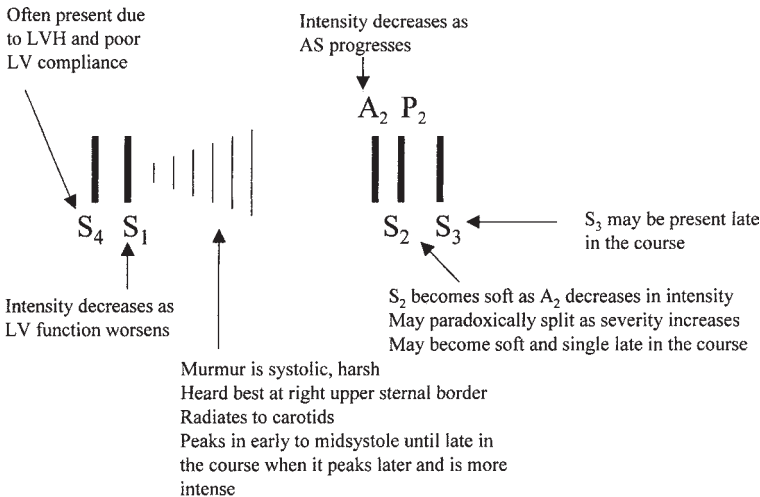


FIGURE 15.2 Auscultatory findings in aortic stenosis. LVH, left ventricular hypertrophy; LV, left ventricular.

TABLE 15.1 Physical Findings and Maneuvers Useful in Distinguishing Various Forms of Left Ventricle Outflow Tract Obstruction

Maneuver finding	Valvular	Supravalvular	Subvalvular	Hypertrophic cardiomyopathy
Pulse volume after PVC	Increases	Increases	Increases	Decreases
Valsalva effect on systolic murmur	Decreases	Decreases	Decreases	Increases
AR	Common	Rare	Common	Rare
S ₄	Common	Uncommon	Uncommon	Common
Carotid pulse	Normal to anacrotic (parvus et tardus)	Unequal	Normal to anacrotic	Rapid jerky upstroke

AR, aortic regurgitation; PVC, premature ventricular contraction

- (2) Careful examination for other murmurs should be performed. AS is often accompanied by AR. Maneuvers performed during the physical examination can help differentiate different types of LV outflow obstruction, whether this is at, below, or above the valve. These are summarized in Table 15.1.

3. Diagnostic testing

- The typical **electrocardiogram (ECG)** of a patient with isolated severe AS usually demonstrates left atrial abnormality (80% of cases) and LVH (85% of cases).
- Chest radiography** can be entirely normal, even in patients with critical AS. The cardiac silhouette may become boot-shaped because of concentric LVH. Cardiomegaly may be identified if there is LV dysfunction or coexisting AR. Aortic valve and root calcification can be seen in adults with severe calcific, degenerative AS. Poststenotic dilation of the ascending aorta may be evident.

- Severity of AS.** The severity of AS is currently graded by ACC/AHA valve guidelines as follows:

Mild: valve area $> 1.5 \text{ cm}^2$, mean gradient $< 25 \text{ mm Hg}$, or jet velocity $< 3.0 \text{ m/s}$

Moderate: valve area **1.0 to 1.5 cm^2** , mean gradient 25 to 40 mm Hg, or jet velocity 3.0 to 4.0 m/s

Severe: valve area $< 1.0 \text{ cm}^2$, mean gradient $> 40 \text{ mm Hg}$, or jet velocity $> 4.0 \text{ m/s}$

The normal aortic valve opens to 3 to 4 cm^2 .

5. Echocardiography

- Transthoracic Doppler echocardiography** is the test of choice per ACC/AHA guidelines to establish the diagnosis of AS, to determine the cause and location, and to assess its severity. It should be performed when the diagnosis of AS is first suspected and information such as LV wall thickness, size, and function should also be obtained. After the diagnosis is established, patients should have frequent, regular clinical follow-up examinations to look for the development of symptoms. Echocardiographic follow-up can be tailored to the severity of disease: at least annually for severe AS and more frequently

as the severity increases. Development of new symptoms and signs should quickly prompt a repeat evaluation.

- (1) The parasternal long-axis views, two dimensional and M-mode, provide valuable information for determining the mechanism and severity of AS. In this view, the coaptation line of the aortic valve is normally centered within the LVOT in a trileaflet valve. The leaflets of a bicuspid valve often have an eccentric closure line, typically posterior to the midline. Systolic leaflet doming can be seen in congenital AS and rheumatic AS. The degree of LVH, LV chamber enlargement, or left atrial enlargement can be quantitated using two-dimensional and M-mode imaging. The LVOT diameter used in the continuity equation is measured in the two-dimensional, parasternal long-axis view.

Subaortic stenosis and supraaortic AS may also be detected in this view. Subaortic stenosis may be evident as a membrane below the aortic valve with normal motion of the valve. Pulsed Doppler may indicate that the obstruction is occurring below the valve and 2 dimensional echocardiogram often shows AR due to the turbulent jet hitting aortic valve leaflets and causing leaflet scarring and impaired coaptation. In supraaortic AS, narrowing above the valve is evident on imaging and with Doppler.

- (2) The parasternal short-axis view is the most useful view for establishing the cause of congenital AS. The number of commissures and the shape of the valve orifice should be assessed (Fig. 15.3). Trileaflet valves open

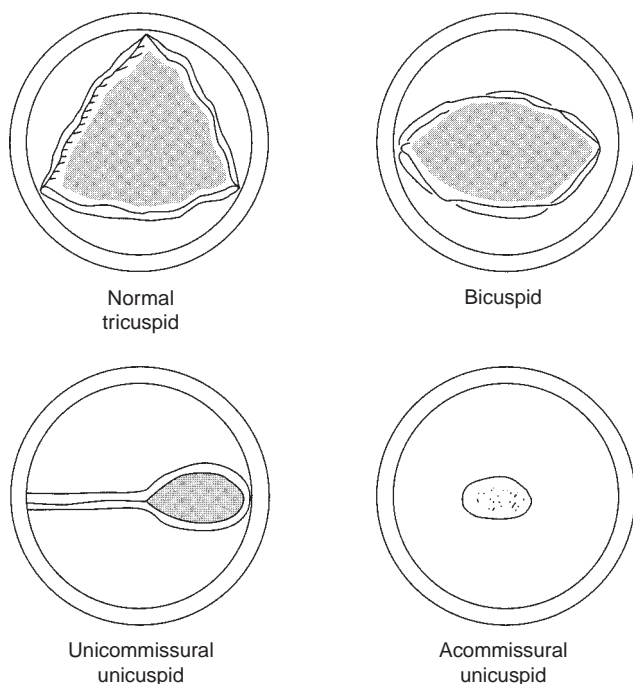


FIGURE 15.3 A schematic representation of parasternal short axis of a congenitally abnormal aortic valve.

as a triangle, whereas an elliptical opening suggests a bicuspid valve. In a unicuspid valve, the opening is elliptical but occurs across a radius rather than the diameter of the valve.

- (3) The apical five-chamber and three-chamber views are well aligned with flow through the aortic valve. Continuous wave Doppler recordings across the aortic valve and pulsed wave Doppler flow in the LVOT proximal to the aortic valve are recorded in these views for the continuity equation.
 - (4) Continuous wave Doppler should be performed at multiple sites, including the suprasternal notch and the right sternal border, to ensure that the maximal velocity across the aortic valve is recorded. The dimensions of the ascending aorta should be measured, and coarctation in the descending aorta should be sought, especially in those with bicuspid aortic valves.
- b. **Transesophageal echocardiography (TEE).** Planimetry of the aortic valve orifice is often possible with TEE and relates well to that measured by cardiac catheterization. Planimetry is difficult when the valve is extremely calcified. In bicuspid valve, the smallest area should be sought carefully, as the valve opening is not planar but rather forms a cone due to the doming of the valve as it opens. TEE is particularly useful for determining the morphologic features of the valve in congenital AS. TEE is often necessary to confirm the diagnosis of subaortic membrane and to differentiate it from hypertrophic cardiomyopathy or valvular AS.
 - c. **Dobutamine echocardiography and stress echocardiography.** Exercise testing in patients with asymptomatic AS may provide useful information such as exercise-induced symptoms or abnormal blood pressure response (ACC/AHA class IIb indication). Exercise testing is contraindicated (ACC/AHA class III indication) in symptomatic patients with AS. Dobutamine echocardiography may be useful in evaluating low-flow/low-gradient AS in patients with LV dysfunction (see Chapter 51 for further discussion).
6. **Hemodynamic calculations**
- a. **Doppler echocardiography** is the standard modality used for the assessment of transvalvular pressure gradient and AVA.
 - (1) **Simplified Bernoulli equation ($\Delta P = 4v^2$)**, in which P is pressure and v is peak velocity of flow across the aortic valve, is used to estimate the peak instantaneous gradient. The mean gradient across the valve can be measured by calculating the area under the Doppler envelope. The peak velocity of flow across the aortic valve should be measured in three areas: the LV apex, the right sternal border, and the suprasternal notch. The highest measured velocity is used to calculate the peak transvalvular gradient. When stenosis is present at two levels (i.e., in LVOT and at the valve), the gradient across the LVOT reflects the integrated effects of the obstruction at both levels. It is usually impossible with Doppler to precisely differentiate the contribution of each level of obstruction to the total. This may be inferred by the analysis of the images, by TEE, or by direct measurement at cardiac catheterization.
 - (2) Calculation of AVA is based on the **continuity principle**, which states that the flow of an incompressible fluid in a closed system must remain constant. Flow in a vessel is the product of the cross-sectional area (A) of the vessel and the velocity (V). Area is calculated as πR^2 or $\pi D^2/4 = 0.785D^2$, where R is the radius of the vessel and D is the diameter. A schematic representation of the variables for calculating AVA is shown in Figure 15.4. The continuity equation for the aortic valve is as follows:

$$\text{Area}_{\text{aortic valve}} = \text{diameter}_{\text{LVOT}}^2 \times 0.785 \times \text{VTI}_{\text{LVOT}} / \text{VTI}_{\text{aortic valve}}$$

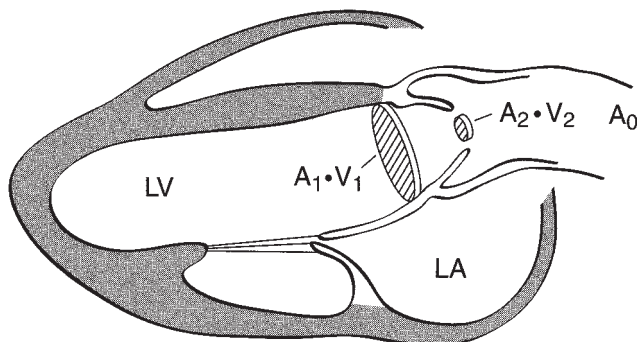


FIGURE 15.4 A schematic representation of parasternal long-axis view and the continuity principle. LV, left ventricle; LA, left atrium.

In the above equation, VTI is the time-velocity integral. The continuity equation is valid only for valvular AS. It cannot be used to assess valve area when there are stenoses in series such as valvular and subvalvular narrowing occurring simultaneously.

- (3) Care should be taken to avoid measuring postextrasystolic beats. If the patient is in atrial fibrillation, 10 consecutive beats should be measured and averaged for both velocity measurements.
- (4) During evaluation of an aortic valve prosthesis, the standard continuity equation cannot be used. Instead, the velocity ratio or **dimensionless index** is used to estimate the severity of prosthetic stenosis. It is calculated by dividing the peak velocity in the LVOT by the peak velocity through the aortic valve. **A dimensionless index of < 0.25 is generally accepted to represent severe stenosis.** This is also useful if the LVOT diameter is difficult to ascertain.
- b. **Cardiac catheterization** was once considered the gold standard for the quantification of AS but is now contraindicated (ACC/AHA class III indication) in the routine evaluation of a patient when echo-Doppler studies are adequate and congruent with clinical findings.
 - (1) Preoperative catheterization. Patients > 50 years of age, patients with angina, and patients with significant risk factors for CAD should undergo coronary cineangiography before aortic valve operations (ACC/AHA class I indication).
 - (2) Catheter-derived hemodynamic data are indicated (ACC/AHA class I indication) to further evaluate the severity of AS when the clinical and echocardiographic findings diverge. Because cardiac catheterization findings often differ from those of echocardiography, it is important to understand the differences in what is being measured. The mean gradients obtained during catheterization should be equivalent to the mean gradients obtained by echocardiography. These correlate well when performed expertly and simultaneously. The peak gradient measured during catheterization is the peak-to-peak gradient, which is lower than the peak instantaneous gradient obtained with echocardiography (Fig. 15.5). In the setting of reduced cardiac output of any cause, the aortic gradient may be much lower and may be < 20 mm Hg in severe LV dysfunction despite critical AS.

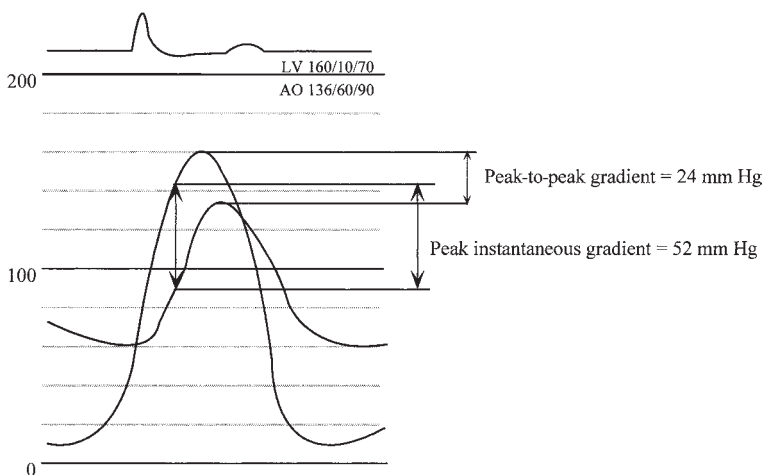


FIGURE 15.5 Simultaneous recording of LV and aortic pressures. LV, left ventricle; AO, aorta.

- (3) The most precise measurement of transaortic valvular gradient is made with two different catheters (one in the LV cavity and the other in the ascending aorta) or with a double-lumen pigtail catheter. Because the two-catheter technique requires cannulation of both femoral arteries, another acceptable method of measuring the peak-to-peak gradient is catheter pullback from the left ventricle to the ascending aorta. A typical pressure tracing of simultaneous LV and aortic pressures is shown in Figure 15.5.
- (4) Catheterization of the patient with severe AS should be performed with low-osmolar, nonionic contrast agents. These cause less hypotension due to peripheral arterial vasodilation, less bradycardia, less transient myocardial dysfunction, and less osmotic diuresis after the procedure. Left ventriculography should be avoided.
- (5) The Gorlin formula is used to estimate AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output} / (44.3 \times \text{heart rate} \times \text{SEP} \times \sqrt{\text{MVG}}).$$

In the above equation, SEP is the systolic ejection period, defined as the time from aortic valve opening to closing (in seconds), and MVG is the mean valvular gradient (mm Hg). The **Gorlin** formula measures the **true anatomic area** of the aortic valve, as it has a correction factor (the discharge coefficient) to account for the difference of flow across the true anatomic valve versus the flow at the level of the vena contracta. **Continuity equation** measures the **physiologic area** (vena contracta) and as such is smaller than that measured by Gorlin.

An alternative measurement can be made by Hakki equation, which is a simplification of Gorlin formula, where the observation of heart rate \times SEP approximates 1,000. This then simplifies the estimation of AVA:

$$\text{AVA (cm}^2\text{)} = \text{cardiac output} / \sqrt{\text{MVG}}.$$

F. Therapy

1. **Medical therapy.** The mainstay of therapy for severe AS is surgical replacement of the aortic valve. Onset of symptoms in patients with severe AS is associated with a marked reduction in lifespan when treated medically, rather than surgically. Medical therapy alone is ineffective for severe symptomatic valvular AS.
 - a. **Antibiotic prophylaxis.** The updated 2007 AHA guideline on prevention of infective endocarditis has been extensively modified. Unless the patient has a valve prosthesis or prior history of infective endocarditis, antibiotic prophylaxis prior to dental procedures is no longer recommended in patients with valvular pathology.
 - b. **Medical therapy in asymptomatic patients.** During the asymptomatic phase, therapy is directed at primary prevention of CAD, maintenance of sinus rhythm, and blood pressure control.
 - c. **Medical therapy in symptomatic patients.** Medical therapies may be necessary in symptomatic patients with severe AS who are awaiting surgery or who are considered inoperable and require palliation. Therapy for heart failure is directed at relief of pulmonary congestion. This is usually achieved with cautious use of diuretics. Overly aggressive diuresis can cause hypotension if hypovolemia significantly impairs cardiac output by diminishing preload. Nitrates can also cause hypotension and syncope by reducing preload and should be avoided or used with extreme caution. Thus, the management of symptomatic patients with AS and CAD is difficult, and urgent surgery is the optimal treatment where feasible. Digoxin is used for symptom relief in the setting of impaired LV systolic function and volume overload, particularly if atrial fibrillation develops.
 - d. **Vasodilator therapy** has been relatively contraindicated in patients with AS, because lowering SVR in the setting of a fixed cardiac output may cause syncope, especially in the ambulatory setting. However, patients with severe heart failure and LV dysfunction with severe AS may benefit from the careful titration of intravenous nitroprusside in the intensive care unit with concomitant invasive arterial and pulmonary artery monitoring. One study suggests an improvement in hemodynamic indices with this approach. This therapy is used only as a bridge to definitive surgical therapy. Intraaortic balloon counterpulsation is another strategy that can be used while patients with LV dysfunction and severe AS in cardiogenic shock are worked up toward urgent surgery.
 - e. **Treatment of hyperlipidemia.** The association between AS and risk factors for atherosclerosis has prompted trials with statins to retard the progression of AS. Several studies suggested that when statin therapy is indicated based on current guidelines for hyperlipidemia it is associated with a modest effect in slowing the rate of progression of AS. However, in more recent randomized controlled trials of patients with calcific AS, where statin therapy was not otherwise mandated, statins had no effect on AS progression. As such, there is currently no indication for statin use specific to AS, although in hyperlipidemic patients with AS, aggressive lowering of LDL level with statins appears warranted. In patients with supravulvar AS due to severe familial hyperlipidemia, improvement in the obstruction may occur after low-density lipoprotein apheresis.
2. **Percutaneous aortic balloon valvuloplasty (PABV) and percutaneous valve replacement**
 - a. In pediatric congenital, noncalcific AS, PABV is a safe and effective therapy, comparable to surgical repair or replacement. The goal of PABV in congenital AS is to achieve a 60% to 70% reduction in the measured peak-to-peak transvalvular gradient. Redilatation or AVR becomes necessary within 10 years of

the initial PABV in > 50% of children. AR is well recognized as a potential early or late complication of PABV, although moderate-to-severe AR occurs in a minority of cases.

- b. In adults, PABV is not an effective long-term therapy for AS compared with surgical AVR. Although PABV initially achieves effective relief of LVOT obstruction (up to 50% improvement in AVA), nearly 50% of patients have restenosis within 6 months. Moreover, PABV does not prolong survival in adults with AS. For these reasons, PABV is mainly used for palliation of symptoms or as a bridge to AVR (ACC/AHA class IIb indication). PABV is generally not recommended in asymptomatic patients with severe AS who are undergoing urgent noncardiac surgery. It is recommended that these patients undergo vigilant monitoring with careful hemodynamic monitoring.
- c. **Percutaneous replacement of the aortic valve.** An exciting strategy currently in development is the placement of a stented bioprosthetic valve over the native aortic valve, either percutaneously from an arterial site (usually in the femoral or iliac artery) or transapically from an incision made at the LV apex on the chest wall (transcatheter aortic valve replacement [TAVR]). The native valve is initially dilated with a balloon. The stented valve is deployed during rapid pacing to allow adequate time for successful placement. Currently, two percutaneous valves are available in the U.S. (Edwards Sapien and CoreValve). Of these, Edwards Sapien valve has gained approval from FDA in 2011 as it has been shown to improve survival in inoperable patients compared to medical therapy. Trials for both valves are currently ongoing. As an option to treat patients who are otherwise not candidates for open surgical replacement, TAVR provides a viable alternative over medical or surgical management. However, the technology is still developing. Paravalvular leak is still common following valve deployment, and the technique has considerable morbidity, not least as it has been used up to now in very ill patients (see Chapter 66).
- 3. **Surgical therapy.** AVR is the surgical treatment of choice. It is preferred over repair because debridement of aortic valve calcification often results in early post-operative AR from leaflet fibrosis and retraction, a process that progresses over time.
 - a. **Recommendations for the use of AVR** in patients with AS according to the modified 2006 ACC/AHA guidelines are given in Table 15.2. The major indications are for severe AS with symptoms or where other cardiac surgery is needed or when LV dysfunction develops as a result of severe AS.
 - b. **Surgical mortality rate** varies among patients with AS depending on age and other comorbidities including concomitant CAD. In an otherwise healthy individual, mortality rate for isolated AVR in experienced centers should be < 1%. When this is the case, the 2006 ACC/AHA guidelines suggest that prophylactic surgical intervention may be considered in severe AS, even in the absence of symptoms, especially if the valve is calcified and therefore the disease is likely to progress rapidly (ACC/AHA class IIb indication).

Successful AVR is feasible and normalizes life expectancy, even in very elderly patients without multiple comorbidities. Surgical options include pulmonary valve autograft (i.e., Ross procedure), aortic valve homograft conduit, a pericardial or porcine bioprosthesis, or a mechanical valve. The relative advantages, disadvantages, and indications for use of the different prostheses are outlined in Chapter 18.

(1) In the Ross procedure, the pulmonary valve and main pulmonary artery are removed as a unit and placed in the aortic position with reimplantation of the coronary arteries. A pulmonary homograft is placed in the pulmonic position. This procedure is best suited for pediatric and adolescent patients

TABLE 15.2 **Recommendations for Aortic Valve Replacement in Patients with Aortic Stenosis**

Class I

- 1 AVR is indicated for symptomatic patients with severe AS
- 2 AVR is indicated for patients with severe AS undergoing CABG or surgery on the aorta or other heart valves
- 3 AVR is recommended for patients with severe AS and LV systolic dysfunction (ejection fraction < 0.50)

Class IIa

AVR is reasonable for patients with moderate AS undergoing CABG or surgery on the aorta or other heart valves

Class IIb

- 1 AVR may be considered for asymptomatic patients with severe AS and abnormal response to exercise (e.g., development of symptoms or asymptomatic hypotension)
- 2 AVR may be considered for adults with severe asymptomatic AS if there is a high likelihood of rapid progression (age, calcification, and CAD) or if surgery might be delayed at the time of symptom onset
- 3 AVR may be considered in patients undergoing CABG who have mild AS when there is evidence, such as moderate-to-severe valve calcification, that progression may be rapid
- 4 AVR may be considered for asymptomatic patients with extremely severe AS (aortic valve area < 0.6 cm², mean gradient > 60 mm Hg, and jet velocity > 5.0 m/s) when the patient's expected operative mortality is 1.0% or less

Class III

AVR is not useful for the prevention of sudden death in asymptomatic patients with AS who have none of the findings listed under the class IIa/IIb recommendations

AVR, aortic valve replacement; AS, aortic stenosis; CABG, coronary artery bypass grafting; LV, left ventricular; CAD, coronary artery disease.

From Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: an executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2006;48: 598–675, with permission from Elsevier.

with growth potential, because the autograft is capable of growth, does not require anticoagulants, and has an excellent hemodynamic profile. The procedure, however, is long and technically difficult and subsequently turns a single-valve problem into a double-valve problem. Problems with pulmonary homograft are common in adults who underwent this operation.

Aortic valve homografts have been used to treat younger patients, especially those who wish to avoid anticoagulation, in the hope that greater durability of this valve might result than with a bioprosthesis. Unfortunately, more recent data suggest that any durability advantage of a homograft over a bioprosthesis in middle-aged patients is slight. Moreover, the homograft tends to calcify and is often difficult to remove at subsequent reoperations. Therefore, enthusiasm for homografts has waned, except in the setting of endocarditis of native or prosthetic valves with pyogenic complications such as abscess or fistula or when the LVOT is small, in which case homografts maximize the flow area and minimize the pressure gradient.

- (2) **Bioprostheses** include porcine heterografts and bovine pericardial prostheses. These valves are most often used to treat patients older than 60 years because structural deterioration is much slower in this age group compared with younger patients. These valves have a low risk for thromboembolism and do not necessitate long-term anticoagulation. Because of the sewing ring and struts, all prostheses, both mechanical and biologic, have a pressure gradient across them, even with normal function. The largest possible valve should be inserted to minimize this pressure gradient. The threshold to insert bioprostheses at a younger age continues to decline given the excellent quality of life these afford.
- (3) **Mechanical valves.** The most commonly used mechanical prostheses include the St. Jude, Medtronic-Hall, and CarboMedics prostheses. These all require anticoagulants to minimize the risk of valve thrombosis and thromboembolism. These valves are durable if anticoagulation is maintained and careful antibiotic prophylaxis is used over the years. Mechanical valves are used with caution in older patients (> 65 years) given the substantial increase in anticoagulation-related hemorrhage and resultant mortality in this population.

G. Special considerations

1. Management of asymptomatic patients with severe AS

- a. **High-risk patients.** Most asymptomatic AS patients have low mortality and morbidity rates. A minority of asymptomatic patients, however, may die suddenly or have rapid progression of disease. These patients may benefit from AVR in the absence of symptoms. Accurate identification of such patients has been difficult. A transaortic flow velocity of > 4 m/s predicts a 70% likelihood of needing an AVR within the subsequent 2 years, whereas a velocity of < 3 m/s corresponds to a low likelihood (< 15%) of needing an AVR in the subsequent 5 years. Patients with highly calcified valves and a rapid increase in the pressure gradient may be considered for elective AVR if the transaortic flow velocity is > 4 m/s. Other reasonable indications for AVR in patients with severe asymptomatic AS include LV dysfunction attributable to AS, exercise-induced hypotension, pulmonary hypertension (> 60 mm Hg), a high likelihood of rapid progression, and before pregnancy.
 - b. **Coronary artery bypass grafting (CABG) in moderate AS.** Is there a need for AVR? Studies suggest a benefit of concomitant AVR in patients undergoing CABG who have an AVA of < 1.5 cm². Although concomitant AVR increases the risk of the initial surgery, the need for reoperation is significantly lower in these patients, and this may provide a survival benefit. Patients with mild AS who have evidence of moderate/severe calcification with a high likelihood of rapid progression may also undergo AVR during CABG.
- #### 2. Patients with AS and severely reduced ejection fraction.
- LV dysfunction in patients with AS can result from the afterload stress imposed on the left ventricle by the stenotic valve or from primary contractile dysfunction (e.g., result of other causes of cardiomyopathy). When LV dysfunction results primarily from afterload mismatch, surgical correction of AS often results in improvement or normalization of LV function. In contrast, patients with primary contractile dysfunction have an overall poor prognosis and are unlikely to benefit from AVR. It is important to determine the cause of LV dysfunction in patients with severe AS for prognostic and therapeutic purposes. These patients should be considered in three major groups: those with high transvalvular gradients (mean gradient > 40 mm Hg), those with low transvalvular gradients (mean gradient < 30 mm Hg), and those with aortic pseudostenosis.
- a. **High transvalvular gradient.** A high transvalvular gradient is a surrogate measure of high afterload mismatch. When the transvalvular gradient is

substantial (e.g., mean gradient > 40 mm Hg), surgical correction of AS can result in normalization of LV function.

- b. **Low transvalvular gradient.** Patients with true anatomically severe AS (AVA < 1.0 cm²) and low transvalvular gradients (mean gradient < 30 mm Hg) have a very poor prognosis without surgery. Despite a substantial operative mortality, survival appears improved in those treated surgically, especially if they demonstrate **contractile reserve** when challenged with dobutamine. Contractile reserve is defined as the ability to increase transvalvular flow by $> 20\%$ from baseline. Dobutamine infusion may help identify the subset of patients with low-gradient AS who benefit from AVR.
- c. **Aortic pseudostenosis.** Patients with primary contractile dysfunction and mild AS can have a falsely small calculated valve area, mimicking severe AS. This phenomenon, called aortic pseudostenosis, occurs principally because the force generated by the weakened left ventricle is not sufficient to open a mildly stenotic valve. Differentiating low-gradient, anatomically severe AS from aortic pseudostenosis is usually accomplished by one of two methods: increasing the cardiac output with dobutamine or decreasing the total peripheral resistance with vasodilators such as nitroprusside. Patients with truly severe AS experience a parallel increase in cardiac output and in the transvalvular pressure gradient after dobutamine infusion (in the echocardiography or catheterization laboratory). The calculated valve area, therefore, does not increase. In contrast, dobutamine infusion in patients with aortic pseudostenosis results in an increase in cardiac output without a significant increase in the transvalvular pressure gradient (the mildly stenotic valve is able to accommodate the increase in blood flow). As a result, the calculated AVA increases significantly (≥ 0.3 cm²). Nitroprusside infusion can also be used to differentiate true stenosis from pseudostenosis by lowering SVR. In true severe AS, the transvalvular gradient increases in response to vasodilators, but the fixed LV outflow obstruction does not allow cardiac output to increase concomitantly. In pseudostenosis, the valve resistance is small, and a decrease in SVR is accompanied by a significant increase in cardiac output and a decrease in the transvalvular gradient. The calculated valve area, therefore, remains the same or decreases in true stenosis and increases in pseudostenosis. The differentiation of true severe AS from aortic pseudostenosis is important because patients with aortic pseudostenosis have primary contractile dysfunction and are unlikely to benefit from AVR alone.
3. **Severe AS with low gradients and preserved left ventricular ejection fraction (LVEF).** Several patients present with severe AS with seemingly normal left ventricular function and paradoxically low gradients. This population appears to be composed of two groups: one with low flow and relatively high afterload and the other in whom the discrepancy between gradients and area may be due to errors in measurement. There is evidence that those with true low flow and severe AS are more likely to be women with small ventricles, significant LVH, and hypertension. In this group, outcome is worse than expected, as surgery may be delayed based on the discrepancy between AVA and gradients even in the presence of symptoms. It is important to be aware of this group and to ensure that those who have severe AS and low flow are considered for early surgery once symptoms occur.
4. **Subaortic stenosis.** Surgical removal of the membrane leading to subaortic obstruction is indicated for symptomatic patients, for asymptomatic patients with a pressure gradient greater than 50 mm Hg, and if there is evidence of concomitant moderate or greater AR as a result of damage to the aortic valve leaflets from the turbulent subvalvular jet.

TABLE 15.3 Major Causes of Chronic Aortic Regurgitation

Leaflet abnormalities	Aortic root or ascending aorta abnormalities
Rheumatic fever	Age-related aortic dilation
Infective endocarditis	Annuloaortic ectasia
Trauma	Cystic medial necrosis of the aorta (isolated bicuspid aortic valve or Marfan's syndrome)
Myxomatous degeneration	Systemic hypertension
Congenital aortic regurgitation	Aortitis (syphilis and giant cell arteritis)
Systemic lupus erythematosus	Reiter's syndrome
Rheumatoid arthritis	Ankylosing spondylitis
Ankylosing spondylitis	Behçet's syndrome
Takayasu's arteritis	Psoriatic arthritis
Whipple's disease	Osteogenesis imperfecta
Crohn's disease	Relapsing polychondritis
Drug-induced valvulopathy	Ehlers-Danlos syndrome

II. AORTIC REGURGITATION

A. Introduction. AR can develop from primary disease of the valve leaflets or from abnormalities of the aortic root or ascending aorta. The chronic and acute forms of AR are distinct disease entities, with different causes, clinical presentations, natural histories, and treatment strategies.

B. Etiology

- 1. Chronic AR.** Disease of the valve leaflets can cause AR by inadequate leaflet coaptation, leaflet perforation, or leaflet prolapse. The most common causes of leaflet abnormalities and aortic root abnormalities that lead to the gradual development of AR are given in Table 15.3. Subaortic stenosis can also cause AR due to a high-velocity jet of blood that is a result of the outflow obstruction hitting the aortic valve, causing damage to the leaflets. Perimembranous ventricular septal defects are associated with AR as well. In addition to disease of native valve leaflets, structural deterioration of bioprosthetic valve leaflets is an important cause of chronic AR.
- 2. Acute AR.** Acute AR can also result from abnormalities in the valve leaflets or in the aortic root. The causes of acute AR are limited (Table 15.4).

TABLE 15.4 Major Causes of Acute Aortic Regurgitation

Leaflet abnormalities	Aortic root or ascending aorta abnormalities
Traumatic rupture	Acute aortic dissection
Acute infective endocarditis	Perivalvular leak or dehiscence of prosthetic valves
Acute prosthetic valve dysfunction	
Post aortic balloon valvuloplasty	

C. Pathophysiology

1. **Chronic AR.** AR results in diastolic regurgitation of LV stroke volume. This produces an increase in LV end-diastolic volume, thereby raising wall tension (i.e., Laplace's law). The ventricle responds to added wall tension by compensatory eccentric hypertrophy of myocytes. As a result, during the chronic compensated phase of AR, the left ventricle is able to adapt to an increase in diastolic volume without a significant increase in end-diastolic pressure. The left ventricle produces a larger total stroke volume with each contraction, preserving normal effective forward stroke volume. Over time, however, progressive interstitial fibrosis reduces LV compliance, leading to the chronic decompensated phase. Chronic volume overload results in impaired LV emptying, an increase in LV end-systolic volume and end-diastolic pressure, further cardiac dilation, and a fall in the ejection fraction and forward cardiac output.
2. **Acute AR.** Acute AR is usually a hemodynamic emergency because the left ventricle does not have sufficient time to adapt to the rapid increase in LV volume. The effective forward stroke volume and cardiac output fall acutely, potentially resulting in hypotension and cardiogenic shock. The sudden increase in LV diastolic pressure initially causes preclosure of the mitral valve in early diastole, protecting the pulmonary vasculature from elevated diastolic pressure. However, further LV decompensation leads to diastolic mitral regurgitation (MR), which allows transmission of elevated diastolic pressure to the pulmonary vascular bed, resulting in pulmonary edema. The tachycardia that accompanies cardiac deterioration helps shorten the diastolic-filling period during which the mitral valve is open.

D. History and clinical presentation

1. **Chronic AR** is usually asymptomatic for a long time. After the development of LV dysfunction, patients gradually experience symptoms related to pulmonary congestion, including increased dyspnea with exertion, orthopnea, and paroxysmal nocturnal dyspnea. LV enlargement frequently produces an uncomfortable sensation in the chest that is exaggerated after premature ventricular contractions and in the supine position. Although angina is uncommon, it can be produced by latent CAD, decreased diastolic coronary perfusion pressure, nocturnal bradycardia and fall in arterial diastolic pressure, marked LVH, and subendocardial ischemia.
2. **Acute AR.** Patients with acute, severe AR usually present with signs of sudden hemodynamic deterioration such as weakness, altered mental status, severe shortness of breath, or syncope. If left untreated, these patients quickly progress to total cardiovascular collapse. When severe chest pain is part of the initial clinical presentation, aortic dissection must be strongly suspected.

E. Physical findings

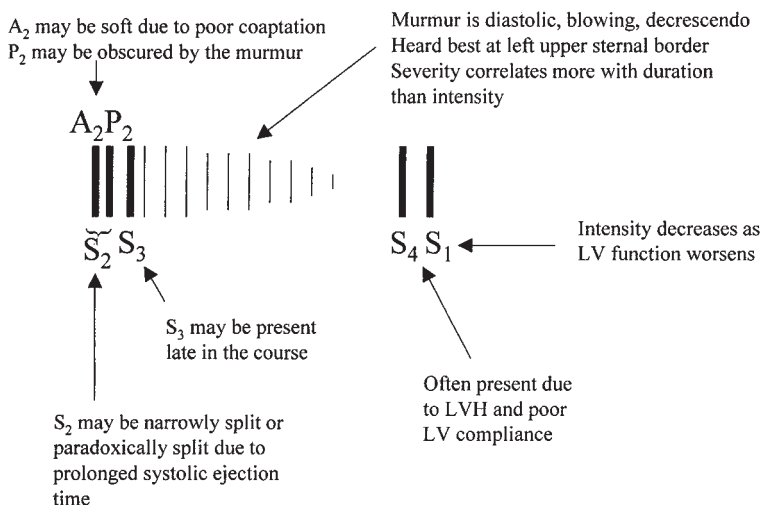
1. **Chronic AR.** Patients with chronic AR can have a wide array of physical findings, especially during examination of the peripheral pulses and cardiac auscultation. The physical examination may yield clues about the cause of AR. Patients with AR should be examined for the peripheral manifestations of infective endocarditis, signs of Marfan's syndrome, evidence of chronic aortic dissection, and signs of collagen vascular disorders.
 - a. **Peripheral pulse examination.** The increased total stroke volume in chronic AR leads to an abrupt increase in arterial pressure during systole, followed by a rapid fall in arterial pressure during diastole. The widened pulse pressure accounts for a number of physical findings associated with chronic AR (Table 15.5). Patients with chronic AR may exhibit a bisferiens pulse, characterized by double systolic peaks with increased amplitude. The signs of hyperdynamic circulation are not specific to AR and can be seen in conditions that cause high-output heart failure, including sepsis, anemia, thyrotoxicosis, beriberi, and arteriovenous fistula.

TABLE 15.5 Physical Signs Associated with Hyperdynamic Pulse in Chronic Aortic Regurgitation

Physical sign	Description
Water hammer or Corrigan's pulse	Rapid upstroke followed by quick collapse
de Musset's sign	Head bob with each heartbeat
Traube's sign	Pistol shot sounds heard over the femoral arteries in both systole and diastole
Müller's sign	Systolic pulsation of the uvula
Duroziez's sign	Systolic murmur over the femoral artery when compressed proximally and diastolic murmur when compressed distally or systolic–diastolic murmur with increasing compression over femoral artery
Quincke's sign	Capillary pulsations visible in the lunula of the nail bed
Hill's sign	Popliteal cuff systolic pressure exceeding brachial cuff systolic pressure by > 60 mm Hg
Becker's sign	Arterial pulsations visible in the retinal arteries and pupils

b. Palpation. With severe AR, the apical impulse is typically enlarged and displaced lateral to the midclavicular line in the fifth intercostal space because of LV enlargement. The impulse may be sustained and hyperdynamic. A diastolic thrill may be palpable in the second left intercostal space, as may a systolic thrill caused by increased aortic flow.

c. Auscultation. The main auscultatory findings are outlined in Figure 15.6.

**FIGURE 15.6** Physical findings in aortic regurgitation. LV, left ventricular; LVH, left ventricular hypertrophy.

- (1) **Heart sounds.** S_1 may be diminished in the presence of PR-interval prolongation, LV dysfunction, or preclosure of the mitral valve. S_2 may be soft, singly split (P_2 obscured by the diastolic murmur) or paradoxically split. An S_3 may be heard with severe LV dysfunction. An S_4 is often present and represents left atrial contraction into a poorly compliant left ventricle.
 - (2) **Diastolic murmur.** The hallmark murmur of AR is a blowing, diastolic, decrescendo murmur that starts immediately after A_2 and is best heard in the left upper sternal border with the patient sitting up and leaning forward slightly in full expiration. In general, the severity of AR correlates with the duration of the murmur more than with its intensity. Early in the course of disease, the murmur is typically short. As the disease progresses, the murmur may become pandsystolic. In the end stages of AR, the murmur may shorten again because of rapid equilibration of pressures in the aorta and left ventricle from an elevated LVEDP. In this situation, other signs of severe AR are usually present.
 - (3) A **second diastolic murmur** may be audible at the apex in severe AR. The Austin Flint murmur is a middle-to-late diastolic rumble that is believed to be caused by vibration of the anterior mitral leaflet as it is struck by the regurgitant jet or by turbulence in the mitral inflow from partial closure of the mitral valve by the regurgitant jet. Unlike the murmur of true valvular mitral stenosis, the Austin Flint murmur is not associated with a loud S_1 or with an opening snap.
 - (4) A short **midsystolic ejection murmur** may be audible at the base of the heart, radiating to the neck. It reflects the increased ejection rate and large stroke volume traversing the aortic valve.
2. **Acute AR.** The physical examination of patients with acute AR differs considerably from that of patients with chronic AR. The physical examination may be most notable for signs of hemodynamic compromise, such as hypotension, tachycardia, pallor, cyanosis, diaphoresis, cool extremities, and pulmonary congestion.
 - a. **Peripheral examination.** The signs of hyperdynamic circulation that characterize chronic AR are often absent in acute AR. The pulse pressure may be normal or only slightly widened. The heart size is often normal, and the point of maximal intensity is not displaced laterally. When aortic dissection is suspected, blood pressures should be taken in all extremities to detect the differences.
 - b. **Heart sounds.** S_1 may be diminished due to preclosure of the mitral valve. Pulmonary hypertension may manifest as an increased P_2 component of the second heart sound. An S_3 often accompanies cardiac decompensation.
 - c. **Murmurs.** The early diastolic murmur of acute AR is shorter and lower in pitch than the murmur of chronic AR. In severe, acute AR, the murmur may not be audible when the diastolic pressure in the left ventricle and aorta equilibrates. The systolic murmur reflecting increased flow across the aortic valve may be heard but is usually not loud. The Austin Flint murmur, if present, is short.
- F. Laboratory evaluation**
1. **ECG.** The typical ECG in chronic AR shows LVH, left-axis deviation, and left atrial abnormality. Conduction abnormalities are unusual but can occur after the development of LV dysfunction. Premature atrial and ventricular beats are common. Sustained supraventricular or ventricular tachyarrhythmias are uncommon in the absence of LV dysfunction or concomitant mitral valve disease. In acute AR, the ECG is usually notable only for nonspecific ST-T-wave abnormalities.

2. **Chest radiograph.** In chronic AR, the chest radiograph may reveal marked cardiomegaly, with the heart being displaced inferiorly and leftward. Dilation of the aortic knob and root may be seen. In acute AR, the LV and left atrial dimensions are usually normal. Aortic dissection can lead to a widened mediastinum and/or a widened cardiac silhouette due to pericardial effusion. The chest radiograph is notable for signs of pulmonary congestion.
3. **Echocardiography.** Two-dimensional and M-mode echocardiography are useful in determining the cause of AR, evaluating the aortic root, and assessing the overall LV size and function. Doppler echocardiography is useful for detecting AR and estimating severity. There are several different methods of estimating the severity of AR with color Doppler, pulsed wave Doppler, and continuous wave Doppler ultrasonography.
 - a. **Two-dimensional and M-mode echocardiography.** The cause of AR can be assessed using two-dimensional echocardiography. Rheumatic AR typically causes thickening and retraction of the leaflet tips, leading to failure of cusp apposition. Bacterial endocarditis, which can cause leaflet fibrosis and retraction, leaflet perforation, or flail of the valve cusp, should be suspected if a vegetation is detected. Prolapse of the aortic valve cusps can occur in many conditions, including infective endocarditis, bicuspid aortic valve, myxomatous degeneration, and Marfan's syndrome. Aortic root abnormalities are also well visualized in the parasternal long-axis view. Aortic root dilation is most often idiopathic, although Marfan's syndrome, Ehlers-Danlos syndrome, ankylosing spondylitis, Reiter's syndrome, rheumatoid arthritis, syphilis, and giant cell arteritis are other potential causes. Symmetric dilation of the aortic root produces a central jet of AR, and focal dilation causes an eccentric jet. In the parasternal long axis, the transducer should be moved up one interspace to assess the ascending aorta. Infective destruction of the aortic wall and proximal aortic dissection flaps may occasionally be visualized on transthoracic images. M-mode echocardiography may reveal **premature closure of the mitral valve in severe, acute AR**. In acute AR and chronic AR, the regurgitant jet can strike the anterior mitral valve leaflet, causing it to reverberate or "flutter" in diastole. Reversed doming of the anterior mitral leaflet may be seen on two-dimensional imaging and generally indicates grade 3 to 4+ AR.
 - b. **Doppler and color flow imaging.** Doppler and color flow echocardiography is used to detect AR and to assess its severity. AR is identified by Doppler imaging as high-velocity pandiastolic flow originating immediately under the aortic valve. Color flow imaging allows the assessment of jet origin, size, and direction. Continuous wave Doppler provides measurement of jet velocity and timing of flow. The maximum length of the AR jet correlates poorly with severity of regurgitation when assessed angiographically. Several other Doppler measures are used to estimate the severity of AR (Table 15.6). The ratio of the jet width to LVOT diameter is measured in the parasternal long-axis view and correlates well with the angiographic severity of AR. The pressure half-time of the aortic regurgitant velocity is defined as the time required for the pressure gradient across the aortic valve to fall to half of its initial value. The pressure half-times of patients with mild, moderate, and severe AR have demonstrated considerable overlap. In general, shorter pressure half-times are associated with increased severity of AR, and a pressure half-time of < 200 milliseconds is nearly always associated with severe AR. Quantitation of regurgitant volume and regurgitant fraction provides the most direct correlation with quantitative angiographic estimates of AR severity. Regurgitant volume is the difference between the stroke volume across the LVOT (representing the sum of forward flow and regurgitant flow) and

TABLE 15.6 Echo-Doppler Assessment of Aortic Regurgitation Severity

	Aortic regurgitation		
	Mild	Moderate	Severe
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet width	Central jet, width < 25% of LVOT	➤ Mild but no signs of severe AR	Central jet, width > 65% LVOT
Doppler vena contracta width (cm)	< 0.3	0.3–0.6	> 0.6
Quantitative (cath or echo)			
Regurgitant volume (mL/beat)	< 30	30–59	≥60
Regurgitant fraction (%)	< 30	30–49	≥50
Regurgitant orifice area (cm ²)	< 0.10	0.10–0.29	≥0.30
Additional essential criteria			
Left ventricular size			Increased

AR, aortic regurgitation; LVOT, left ventricular outflow tract.

From Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: an executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2006;48:598–675, with permission from Elsevier.

that across the mitral valve inflow (representing forward flow), provided there is no significant MR. The regurgitant fraction is the ratio of the regurgitant volume divided by the LVOT stroke volume. The proximal isovelocity surface area (PISA) method is also used for estimating AR severity. The PISA method is used to calculate the effective regurgitant orifice (ERO) area. An ERO area ≥ 0.30 cm² is indicative of severe AR. The presence of a proximal convergence area on transthoracic echocardiogram at the aortic valve is indicative of at least moderate AR. Pulsed wave Doppler echocardiography should be performed in the proximal descending aorta to establish the presence of diastolic flow reversal. Some degree of flow reversal is normally seen early in diastole due to reflux of blood into the coronary vasculature, but if this is > 40 cm/s and continues throughout diastole, then severe AR is likely, especially if this persists in the abdominal aorta. Flow reversal may also be seen with other conditions that cause blood to leak out of the arterial system such as patent ductus arteriosus or sizeable arteriovenous fistula.

- c. **TEE** is used to rule out vegetation or aortic valve ring abscess in patients who may have bacterial endocarditis. In pure AR, vegetation typically occurs on the LV side of the aortic valve. TEE is also used to visualize congenital valvular abnormalities (e.g., bicuspid valve) and to exclude aortic dissection.
- d. **Stress echocardiography** is useful for assessing the ability to exercise. However, a fall in LVEF on exercise is less predictive of occult contractile dysfunction in severe AR than it is in MR. In AR, afterload often increases substantially on exercise, precipitating a fall in ejection fraction. A fall in LVEF on stress echocardiography alone is not a primary indication for valve surgery.

- 4. Cardiac catheterization.** Cardiac catheterization is not necessary for all patients with chronic AR unless there are concerns about AR severity, hemodynamic abnormalities, or LV function, despite noninvasive testing and the physical examination. All patients older than 50 years with severe AR should undergo coronary cineangiography before any definitive surgical procedure on the valve to detect CAD. The decision to perform cardiac catheterization in younger patients should be made on an individual basis after assessment of the patient's cardiac risk profile. Catheter manipulation in patients with AR may be difficult because of dilation of the ascending aorta. Caution should be exercised when manipulating catheters in patients with Marfan's syndrome or cystic medial necrosis of the aortic wall to minimize the risk of vascular trauma. In addition to conventional coronary cineangiography, aortography should be performed to evaluate the degree of AR. The grading of AR by angiography is given in Table 15.7. Right heart catheterization may be helpful in certain circumstances, such as new-onset heart failure or combined AR and AS.
- G. Natural history.** Moderate-to-severe AR may have a good prognosis for many years, provided the patient is asymptomatic and does not exhibit signs of LV dysfunction or severe dilation. Asymptomatic patients with normal LV function require AVR at a rate of only 4% per year. Ninety percent of such patients remain asymptomatic at 3 years, 81% at 5 years, and 75% at 7 years after the diagnosis is made. Patients with mild-to-moderate AR have had a 10-year survival rate of 85% to 95%. Patients with moderate-to-severe AR treated with medical therapy have a 5-year survival rate of 75% and a 10-year survival rate of 50%. After the development of LV dysfunction, progression to symptoms is greatly accelerated, with rates approaching 25% per year. When symptoms develop, there is a rapid decline in functional status. Without surgical intervention, symptomatic patients usually die within 4 years of the onset of angina and within 2 years of the onset of heart failure. Sudden death may occur among patients with severe, symptomatic AR. Sudden cardiac death is frequently the result of ventricular arrhythmias that are primary (in the context of LVH or dysfunction) or secondary, resulting from myocardial ischemia. It has become clear that the various dimensions used to guide surgery in AR are relative and should be interpreted in the context of patient size and gender.
- H. Therapy**

1. Medical therapy

a. Chronic AR

- (1) Medical therapy.** Vasodilators, such as hydralazine, angiotensin-converting enzyme (ACE) inhibitors, and calcium channel blockers, have been used in the treatment of chronic AR to reduce the severity of regurgitation and help delay surgical intervention. There is conflicting evidence of their value (Table 15.8). Current ACC/AHA guidelines contraindicate their use (ACC/AHA class III indication) as an alternative to surgery when surgical intervention is indicated in a patient with acceptable surgical risk.

TABLE 15.7 Angiographic Grading of Aortic Regurgitation

Degree of aortic regurgitation	Left ventricular opacification	Rate of clearing
Mild (1+)	Faint, incomplete	Rapid
Moderate (2+)	Faint, complete	Rapid
Moderate to severe (3+)	Equal to aortic opacification	Intermediate
Severe (4+)	Greater than aortic opacification	Slow

TABLE 15.8 **Indications for Vasodilator Therapy in Chronic Severe Aortic Regurgitation**

Indication	Class
Chronic therapy in patients with severe regurgitation who have symptoms and/or LV dysfunction when surgery is not recommended because of additional cardiac or noncardiac factors	I
Short-term therapy to improve the hemodynamic profile of patients with severe heart failure symptoms and severe LV dysfunction prior to proceeding with AVR	IIa
Long-term therapy in asymptomatic patients with severe regurgitation who have LV dilation but normal systolic function	IIb
Not indicated for long-term therapy in asymptomatic patients with mild-to-moderate AR and normal LV systolic function	III
Not indicated for long-term therapy in asymptomatic patients with LV systolic dysfunction who are otherwise candidates for valve replacement	III
Not indicated for long-term therapy in symptomatic patients with either normal LV function or mild-to-moderate LV systolic dysfunction who are otherwise candidates for valve replacement	III

AR, aortic regurgitation; AVR, aortic valve replacement; LV, left ventricular.

From Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: an executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2006;48:598–675, with permission from Elsevier.

Vasodilators are recommended in nonsurgical candidates with severe, chronic AR who develop symptoms or LV dysfunction (ACC/AHA class I indication). Vasodilators may also be reasonable for short-term therapy, improving the hemodynamics in patients with severe heart failure and LV systolic dysfunction prior to AVR. In asymptomatic patients, long-term vasodilator therapy may be considered for those with severe AR and normal LV systolic function who begin to demonstrate LV dilation. Long-term vasodilator therapy is not recommended for asymptomatic patients with mild-to-moderate AR and normal systolic function. These patients have a good prognosis and do not appear to benefit from vasodilator therapy. Although asymptomatic patients with LV systolic dysfunction or symptomatic patients may be treated with vasodilators in the short term, appropriate surgical candidates should be referred for AVR, and vasodilators should be continued on a long-term basis only if LV systolic dysfunction persists after AVR. The evidence for the use of specific vasodilator agents has been variable. Hydralazine was found to improve LV systolic function and to reduce LV chamber dimensions in some studies. Nifedipine was found to reduce LV volume and increase LVEF in a group of asymptomatic patients who were followed for 1 year. When compared with digoxin, nifedipine slowed the progression of LV dysfunction and delayed the time to surgical treatment in an unblinded, randomized study over a 5-year period. ACE inhibitors have been shown to decrease LV volume in some studies. However, the benefits of ACE inhibitor therapy were seen only when blood pressure was effectively lowered.

- (2) In patients with significant aortic root dilation as a result of cystic medial necrosis or related conditions, treatment with a β -blocker should be considered to slow the rate at which the aortic root enlarges. This has been proved to be beneficial in Marfan's syndrome and is also indicated in patients with bicuspid AV and dilated aortic roots without moderate or severe AR. Angiotensin receptor blockers have also been associated with reduction in progression of aortic disease and should be considered in patients with Marfan-related syndromes. When aortic root dilation is larger than 5 cm in severe AR (lower in Marfan's syndrome), aortic valve surgery and root replacement are indicated.

b. Acute AR

- (1) The goal of **medical therapy** in acute AR is hemodynamic stabilization before proceeding with surgical correction. For patients presenting with cardiogenic shock, intravenous vasodilators are used to reduce the afterload stress on the left ventricle, to lower LVEDP, and to augment forward cardiac output. In severe cases, intravenous inotropic agents may be required for temporary hemodynamic support. β -Blockers may be used with caution when acute AR is caused by an aortic dissection. β -Blockers help reduce arterial dP/dt , which reflects the transmission of force from LV ejection to the arterial wall. Although this is an essential component of the treatment of acute aortic dissection, β -blockers increase the length of diastole by slowing the heart rate, which can exacerbate acute AR and contribute to cardiovascular collapse.
 - (2) A **surgical evaluation** should be performed immediately for a patient with AR caused by aortic dissection or chest trauma. The goal of medical therapy in this setting is to maximize forward cardiac output and minimize propagation of aortic dissection if present.
 - (3) If acute AR is associated with **endocarditis**, antibiotic therapy should be instituted as soon as all culture specimens are obtained.
2. **Percutaneous therapy.** *Insertion of an intraaortic balloon counterpulsation device in patients with more than moderate AR or in the presence of aortic dissection is contraindicated.* Patients with combined AS and AR are poor candidates for PABV because the degree of AR is likely to increase after the procedure.
 3. **Surgical therapy**
 - a. **Chronic AR.** The ACC/AHA guidelines on the indications for AVR in patients with chronic AR are given in Table 15.9.
 - (1) **Symptomatic patients.** The updated ACC/AHA guidelines state that AVR is recommended for symptomatic patients with severe AR regardless of the ejection fraction.
 - (2) The indications for AVR in **asymptomatic patients** remain controversial. AVR is recommended when patients with chronic severe AR are undergoing any other open heart surgery. Asymptomatic patients with chronic, severe AR and LV systolic dysfunction (ejection fraction < 50%) are at high risk for the development of symptomatic heart failure within 2 to 3 years and, therefore, should be considered for elective surgical intervention. Asymptomatic patients with normal LV systolic function at rest and evidence of severe LV dilation (LV end-diastolic dimension > 75 mm and end-systolic dimension > 55 mm) have an increased risk of sudden cardiac death. Their prognosis after AVR, however, is excellent, and they should be referred for valve replacement. When patients with severe LV dilation develop symptoms or LV systolic dysfunction, the perioperative mortality rate increases significantly. AVR is not recommended in asymptomatic patients with normal systolic function at rest and normal or mildly abnormal LV dimensions (end-diastolic

TABLE 15.9 Indications for Aortic Valve Replacement in Severe Aortic Regurgitation

Indication	Class
Symptomatic patients with severe AR irrespective of LV systolic function	I
Asymptomatic patients with chronic, severe AR and LV systolic dysfunction (EF < 50%) at rest	I
Patients with chronic, severe AR undergoing coronary artery bypass surgery or surgery on the aorta or other heart valves	I
Asymptomatic patients with severe AR and EF > 50%, but with severe LV dilation (EDD > 75 mm or ESD > 55 mm ^a)	IIa
Patients with moderate AS while undergoing surgery on the ascending aorta or coronary artery bypass grafting surgery	IIb
Asymptomatic patients with severe AR and normal LV systolic function (EF > 50%) when the EDD > 70 mm or ESD > 50 mm, when there is evidence of progressive LV dilation ^a , declining exercise tolerance or abnormal hemodynamic responses to exercise	IIb
AVR not indicated for asymptomatic patients with mild, moderate, or severe AR and normal LV systolic function at rest (EF > 50%) and when degree of dilation is not severe (EDD < 70 mm and ESD < 50 mm)	III

AR, aortic regurgitation; LV, left ventricular; EF, ejection fraction; EDD, end-diastolic dimension; ESD, end-systolic dimension; AS, aortic stenosis.

^aConsider lower threshold values for patients of small stature of either gender.

From Bonow RO, Carabello B, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: an executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2006;48:598–675, with permission from Elsevier.

dimension < 70 mm and end-systolic dimension < 50 mm). However, in practice, few physicians wait until the LV end-diastolic dimension is 75 mm or the end-systolic dimension is 55 mm to consider surgical intervention even if the patient remains asymptomatic. Most physicians weigh up the benefit and risk to the individual patient and err on sending the asymptomatic patient to surgery at a lower end-systolic dimension (usually 50 mm) and may opt to intervene even earlier in patients of smaller body size and height.

- (3) The **surgical alternatives** are discussed in **Section I**. **Many patients with prolapse of bicuspid valve as the cause of AR may be candidates for surgical repair of the aortic valve.** Some patients with leaflet perforation caused by infectious endocarditis may be candidates for repair in which a pericardial patch is sewn over the defect.
- (4) Postoperatively, patients with severe AR may show initial worsening in LV function despite relative normalization of LV size. This is likely due to the hemodynamic changes produced by eradicating the regurgitation. Slow improvement with normalization or at least stabilization of function at about 6 months is common in these patients. Afterload reduction is indicated postoperatively in patients with impaired LV systolic function at least until there is normalization of LV systolic function.

4. **Follow-up care.** Patients with chronic AR should be observed closely for the development of LV systolic dysfunction. Follow-up evaluation is typically conducted with serial echocardiography. When signs of LV systolic dysfunction manifest, consideration should be given to surgical therapy, even if the patient has no symptoms. Routine postoperative care is appropriate after AVR or repair is completed.
5. **Key suggestions**
 - a. Acute, severe AR is usually a surgical emergency. Signs of congestive heart failure and mitral valve preclosure are ominous in acute AR.
 - b. Valve replacement can be performed without infection of the prosthesis in active endocarditis, even when antibiotics have only recently been started. An aortic valve homograft is the preferred prosthesis in the setting of endocarditis.
 - c. Aortic dissection should be suspected in any patient with chest pain and AR.
 - d. If LV systolic dysfunction is present for < 18 months, LV function is likely to improve postoperatively.
 - e. Heart rate is usually normal until late in the course of disease, when a low effective stroke volume is compensated with tachycardia to maintain cardiac output.
 - f. Rapid atrial or ventricular pacing may be used as a temporary measure to manage acute AR caused by endocarditis or trauma to improve cardiac output. The diastolic-filling phase is shorter at higher heart rates; therefore, there is less time for valvular regurgitation.

ACKNOWLEDGMENTS: *The authors would like to thank Dr. Anne Kanderian and Dr. Anjli Maroo for their work in the previous editions.*

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Mitral Valve Disease

I. INTRODUCTION

- A. The **mitral valvular apparatus** consists of the anterior and posterior leaflets, the mitral annulus, the chordae tendineae, and the papillary muscles (PMs).
 - 1. Normal function of the apparatus brings both leaflets together in systole, creating the coaptation zone.
 - 2. The anterior portion of the mitral annulus is in continuity with the fibrous skeleton of the heart, making it less prone to dilation than the posterior annulus.
 - 3. The coaptation line of the anterior and posterior leaflets is located in the posterior one-third of the valve orifice.
 - 4. The middle scallop of the posterior leaflet is designated P_2 , with the lateral scallop designated P_1 and medial scallop designated P_3 . The corresponding areas of the anterior leaflet are designated A_1 , A_2 , and A_3 .
 - 5. The mitral valve leaflets are attached via the chordae tendineae to the PMs, which are part of the left ventricle.
- B. Mitral regurgitation (MR) can occur as a result of malfunction of any of these components.
- C. Mitral valve prolapse (MVP) exists when one or both mitral leaflets extend beyond the plane of the mitral valve annulus into the left atrium during systole.
- D. Mitral stenosis (MS) is usually valvular and is caused more rarely by the fusion of subvalvular components.

II. MITRAL REGURGITATION

A. Clinical presentation

1. Signs and symptoms

- a. With **acute, severe de novo MR**, an abrupt rise in pulmonary capillary wedge pressure (PCWP) causes pulmonary edema. The symptoms include rest dyspnea, orthopnea, and possibly signs of diminished forward flow, including cardiogenic shock.
- b. Chronic MR is usually **asymptomatic** for years. The most common presentation is an asymptomatic murmur. **When symptoms develop**, exercise intolerance and exertional dyspnea usually occur first. Orthopnea and paroxysmal nocturnal dyspnea may develop as MR progresses. Fatigue is caused by diminished forward cardiac output. With the development of left ventricular (LV) dysfunction, further symptoms of congestive heart failure (CHF) are manifest. **Long-standing severe MR** may cause **pulmonary hypertension**, with symptoms of right ventricular (RV) failure. Atrial fibrillation commonly occurs as a consequence of left atrial (LA) dilation.

2. Physical findings

- a. **Inspection and palpation.** When LV function is preserved, carotid upstrokes are sharp, and the cardiac apical impulse is brisk and hyperdynamic. An early diastolic LV filling wave may be palpable because of the

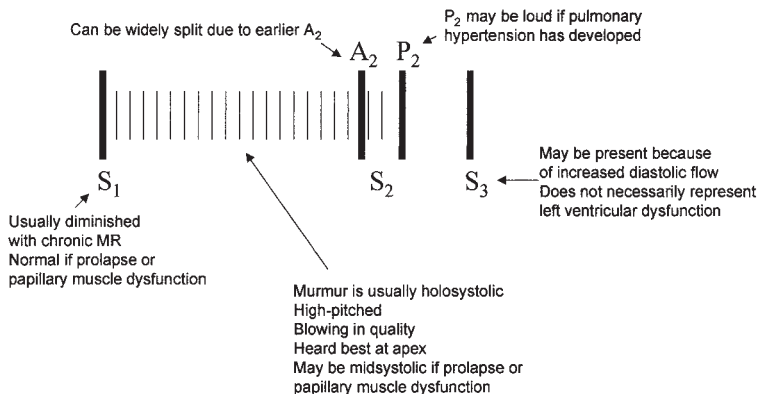


FIGURE 16.1 Auscultatory findings in mitral regurgitation.

large volume of blood traversing from the left atrium to the left ventricle. A late systolic thrust may be present in the parasternal location because of systolic expansion of the left atrium (which may be difficult to differentiate from an RV lift). With the development of LV dilation, the apical impulse is displaced laterally. An RV heave and a palpable P_2 are present if pulmonary hypertension has developed. An elevated jugular venous pressure, hepatomegaly, ascites, and peripheral edema indicate secondary RV dysfunction.

- b. Auscultation.** The main auscultatory findings are shown in Figure 16.1. A loud S_1 (not illustrated) can be heard sometimes, particularly with acute MR. In acute, severe MR, the systolic driving pressure across the mitral valve is reduced due to a high LA pressure and, as a result, the murmur is short and relatively soft. If the LA pressure is markedly elevated, the murmur of acute MR may be inaudible. With decompensated systolic heart failure, fine inspiratory pulmonary crackles may be evident.
- 3. The differential diagnosis of holosystolic murmurs** includes MR, tricuspid regurgitation, and ventricular septal defect (VSD). All are high pitched, but the murmur of a VSD is often harsh in quality, unlike the blowing murmurs of MR and tricuspid regurgitation.
 - a.** The murmur of **MR** is best heard in the apical position and often radiates to the axilla (although possibly to the base with anteriorly directed jets); those of tricuspid regurgitation and VSD typically do not. The murmur of posteriorly directed MR radiates to the back.
 - b.** Tricuspid regurgitation is best heard at the left lower sternal border and radiates to the right of the sternum and left midclavicular line. Like all right-sided murmurs, tricuspid regurgitation is accentuated by inspiration.
 - c.** A **VSD** murmur is heard at the left sternal border and often radiates throughout the precordium.
- B. Etiology and pathophysiology.** MR is more commonly myxomatous or ischemic, rather than rheumatic, in etiology. The causes of MR are summarized in Table 16.1.
 - 1.** In **acute MR**, the regurgitant volume that returns from the left atrium causes a **sudden increase in LV end-diastolic volume**. The left ventricle compensates for this by means of the Frank-Starling mechanism: increased sarcomere length (preload) enhances LV contraction (inotropy). This occurs at the cost of

TABLE 16.1 Causes of Mitral Regurgitation**Leaflet abnormalities**

Myxomatous degeneration of leaflets with excessive motion (most common)

Rheumatic disease: scarring and contraction lead to the loss of leaflet tissue

Endocarditis: can cause leaflet perforations and retraction in the healing phase

Aneurysms: usually from aortic valve endocarditis; aortic insufficiency produces jet lesion on the mitral valve

Congenital:

Cleft mitral valve: isolated or with ostium primum atrial septal defect

Double-orifice mitral valve

Hypertrophic cardiomyopathy: systolic anterior motion of the mitral valve

Mitral annular abnormalities

Annular dilation

From left ventricular dilation: dilated cardiomyopathy, ischemic disease, hypertension

Normal 10 cm in circumference

With sufficient dilation, loss of adequate leaflet coaptation

Tethering of leaflet and chordae can occur and produce relative restriction of leaflet motion

Mitral annular calcification

Degenerative disorder, most commonly seen in the elderly

Accelerated by hypertension or diabetes

Also seen in renal failure with dystrophic calcification

Also seen with rheumatic heart disease

Marfan syndrome and Hurler syndrome

Mitral regurgitation results from immobility of the annulus and loss of sphincter activity

Chordal abnormalities

Chordal rupture (most severe form is flail leaflet) results in loss of leaflet support usually with myxomatous degeneration

Rheumatic heart disease (chordal fibrosis and calcification)

Papillary muscle abnormalities

Rupture with myocardial infarction

Complete rupture typically not survived

Partial rupture more typically encountered

Dysfunctional papillary muscle

Ischemia

Posteromedial papillary muscle, single blood supply through posterior descending artery

Anterolateral papillary muscle, supplied by left anterior descending artery and left circumflex artery

Infiltrative processes: amyloid and sarcoid

Congenital: malposition, parachute mitral valve

increasing LV filling pressure and may cause symptoms of pulmonary congestion. LV wall stress (afterload) is reduced because blood is ejected into the lower pressure left atrium as well as into the systemic circulation. Increased inotropy and reduced afterload cause more complete LV emptying and hyperdynamic function. Forward cardiac output declines, however, because much of the flow is directed to the left atrium. If the acute hemodynamic insult is tolerated, the patient's condition **may progress to a chronic compensated state**.

2. In **chronic compensated MR**, there is **dilation of the left ventricle with eccentric hypertrophy**.

- a. Wall stress is normalized with the development of hypertrophy. Afterload reduction by the low-resistance left atrium is not as significant as it is in the acute phase. Preload remains elevated by the same mechanism as in acute MR. LA dilation helps to accommodate the increased preload at lower filling pressures. LV function is not as hyperdynamic as in the acute state but is in the high-normal range.
 - b. Patients may stay in this asymptomatic or minimally symptomatic phase for years; however, **contractile dysfunction may develop insidiously** during this phase. Increased preload, normal or decreased afterload, and increased sympathetically mediated contractility all continue to augment the ejection fraction (EF). However, as the regurgitant volume ejected back into the left atrium diminishes the actual forward stroke volume (SV), the EF may over-represent cardiac output.
3. In **chronic decompensated MR**, there is LV dysfunction along with progressive enlargement of the LV chamber with increased wall stress. LV dysfunction and enlargement increase the severity of MR, further contributing to the cycle of deterioration. **Irreversible LV contractile dysfunction** may be present by the time overt symptoms develop and this confers higher rates of postoperative heart failure and increased mortality.

C. Laboratory examination

1. The **electrocardiographic** findings are **nonspecific**. The principal features are LA enlargement and atrial fibrillation. LV hypertrophy and RV hypertrophy may also be seen in patients with severe MR.
2. Chest radiography. Cardiomegaly with LA and LV enlargement may be seen in chronic MR. Interstitial edema, manifest as Kerley B lines, followed by alveolar edema may develop in acute cases or with progressive LV failure. Calcification of the mitral annulus may be visualized as a C-shaped opacity in the lateral projection.

D. Diagnostic testing

1. Echocardiography plays a pivotal role in the evaluation of MR. It is useful in **diagnosing MR and in determining its severity and cause**. MR **severity is graded semiquantitatively as follows**: 1+ for mild, 2+ for moderate, 3+ for moderately severe, and 4+ for severe regurgitation. Increasingly, **MR is quantified where feasible**. This is accomplished most often using the proximal convergence method (see below). Quantification provides prognostically powerful information that is less affected by the ongoing loading conditions.

The American College of Cardiology/American Heart Association (ACC/AHA) class I recommendation is for the use of Doppler echocardiography to determine the mechanism and severity of MR, to assess the LA and LV size and function over time, to assess the pulmonary artery (PA) pressures, and to reevaluate periodically if more than mild, and after mitral valve surgery. The current ACC/AHA classification of MR severity by Doppler echocardiography is summarized in Table 16.2.

- a. Color Doppler echocardiography allows the diagnosis of MR by means of visualization of the regurgitant jet or jets entering the left atrium and allows the assessment of severity.
 - (1) Jet length and area are used in this assessment. These measurements are **reliable with central jets**, but underestimation of MR may occur with eccentric jets. Because a jet directed against the atrial wall appears smaller than a free jet of the same regurgitant volume (Coanda effect), it is common practice to upgrade the estimated severity of MR by at least one grade in this situation. The direction of the MR jet can also aid in assessing the

TABLE 16.2 Assessment of Severity of Mitral Regurgitation

	Mild	Moderate	Severe ^a
Qualitative			
Angiographic grade	1+	2+	3–4+
Color Doppler jet area	Small, central jet (< 4 cm ² or < 20% LA area)	Signs of MR > mild present, but no criteria for severe MR	Vena contracta width > 0.7 cm with large central MR jet (area > 40% of LA area) or with a wall-impinging jet of any size
Doppler vena contracta width (cm)	< 0.3	0.3–0.69	≥0.70
Quantitative (cath or echo)			
Regurgitant volume (mL/beat)	< 30	30–59	≥60
Regurgitant fraction (%)	< 30	30–49	≥50
Regurgitant orifice area (cm ²)	< 0.20	0.2–0.39	≥0.40

^aIn severe MR, evidence of LA and LV dilation is essential.

MR, mitral regurgitation; LA, left atrium; LV, left ventricle.

Adapted from 2006 Valve Disease ACC/AHA Guidelines.

cause of MR (Table 16.3). Regurgitation caused by prolapse or flail (excessive leaflet motion) results in a jet direction opposite to the affected leaflet (i.e., posterior jet with anterior leaflet prolapse). MR caused by leaflet restriction (rheumatic and ischemic) is directed toward the affected leaflet.

(a) Caveats

- i. MR is assessed with **transesophageal echocardiography (TEE)**. Patients often receive sedation before TEE, and the sedation may reduce systemic blood pressure (afterload). This could make the MR appear less severe than it is under normal physiologic circumstances. This effect of sedation may be mitigated to some extent by increasing the afterload by handgrip or by the cautious administration of phenylephrine.

- ii. In the evaluation of MR in the **intraoperative setting**, there may be fluctuations in afterload and preload.

- (b) Multiple factors, such as hemodynamic considerations, geometric factors (constraint imposed by the LA wall), and instrumentation, may affect color Doppler measurements. This has led to the development of other measurements to quantify MR.

- (2) The width of the vena contracta, which is the narrowest portion of the proximal regurgitant jet downstream from the orifice, is a **reliable indicator of the severity of MR**. A width **≥0.70 cm suggests severe MR**. High-resolution and zoom images must be used for an accurate

TABLE 16.3 Mechanisms, Direction of Color Jet, and Surgical Management of Mitral Regurgitation

Jet direction	Leaflet motion	Likely cause	Surgical method
Anterior	Excessive	Posterior leaflet prolapse	Quadrilateral resection Annuloplasty Chordal shortening Shortening of papillary muscle
Posterior	Restricted	Anterior leaflet restriction	Debridement
	Excessive	Anterior leaflet prolapse	Chordal transfer or shortening
		Posterior leaflet resection to move coaptation apically	
	Restricted	Posterior leaflet restriction	Debridement, annuloplasty
Central	Normal	Ventricular dilation	Annuloplasty
	Excessive	Bileaflet prolapse	Resection, chordal transfer
	Restricted	Bileaflet restriction	Debridement
Commissural	Normal	Ventricular dilation	Annuloplasty
	Papillary muscle dysfunction		Reattach or fold papillary muscle
	Eccentric	Perforation or cleft	Pericardial patch

From Stewart WJ. Intraoperative echocardiography. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott–Raven Publishers; 1998, with permission.

assessment of the vena contracta or else TEE may be needed. There is some tendency for overestimation of the width of the vena contracta because of limited lateral resolution.

- b. Pulsed-wave Doppler echocardiography of pulmonary venous flow may be useful in the assessment of the severity of MR (Fig. 16.2). Sampling of the pulmonary veins results in three distinct waves: a systolic antegrade wave, a smaller diastolic antegrade wave, and a small negative wave that represents atrial reversal during atrial contraction. With increasing MR, there is a progressive decrease in the systolic wave of pulmonary inflow with eventual reversal. **Blunting of the systolic component** of pulmonary venous flow in the presence of normal LV function suggests at least moderately severe MR. **Systolic flow reversal** suggests severe MR. Blunted pulmonary venous flow is a less reliable indicator of substantial MR in the setting of atrial fibrillation or severe LV dysfunction, since these conditions also can cause systolic blunting.
- c. **Pulsed-wave Doppler echocardiography of mitral inflow.** SV across the regurgitant mitral valve can be estimated and compared with the SV derived from pulsed-wave Doppler imaging across a competent valve (such as the aortic or pulmonary valve). The excess flow at the mitral valve over that

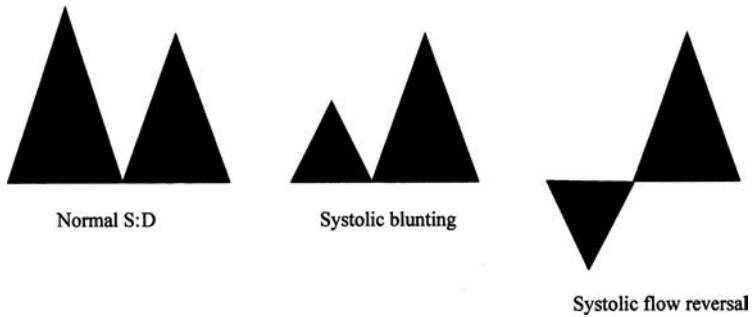


FIGURE 16.2 Patterns of pulmonary venous flow. *First triangle* in each panel represents flow during systole. *Second triangle* represents flow during diastole. The three potential patterns are displayed: normal flow ratio, blunted systolic flow, and reversed systolic flow.

derived at the aortic valve is **the regurgitant volume**. These methods are both tedious and technically difficult.

- d. The **proximal isovelocity surface area (PISA)** or flow convergence method provides a quantitative assessment of MR (see Fig. 16.3 and Chapter 67). Peak mitral flow rate is derived as follows:

$$QFC = 2\pi r^2 V$$

where r is the radius of the shell and V is the aliasing velocity at that shell. **Regurgitant orifice area (ROA)**, a relatively load-independent measure of regurgitation, is derived from peak flow rate by dividing this by peak flow velocity (maximal MR continuous-wave velocity, V_{mr}):

$$ROA = 2\pi r^2 V / V_{mr}$$

The **regurgitant volume** (RV) may be further calculated by the equation $ROA \times VTI_{mr}$, where VTI_{mr} is the velocity–time integral of the regurgitant jet.

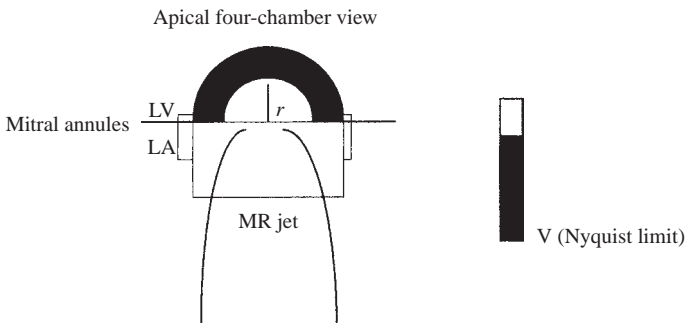


FIGURE 16.3 The proximal isovelocity surface area method for determining severity of mitral regurgitation (MR). LV, left ventricle; LA, left atrium.

If the forward SV is known, then the **regurgitant fraction** (RF%) may be derived as follows:

$$RF = RV / (RV + SV)$$

SV may be estimated in the LV outflow tract as $\text{area} \times \text{VTI}$, as performed in the continuity equation (see Chapter 15).

ROA has been shown to be prognostically powerful in MR of ischemic or degenerative origin. **An ROA of 0.4 cm^2** or greater is indicative of severe MR.

(1) **Simplified** proximal convergence method. The preceding calculation may be simplified to allow the ROA to be estimated with only one measurement. Using this method, MR velocity is assumed to be 5 m/s and the aliasing velocity is set at 40 cm/s. The ROA may be calculated as $v^2/2$. **Higher ROA indicates an increased severity of MR.**

(2) Inaccuracies in using proximal convergence method occur when the orifice is nonspherical, multiple jets are present, or the flow convergence zone is constrained as occurs with eccentric jets. The latter situation occurs with a flail leaflet, as regurgitant flow and ROA are typically overestimated by the use of the PISA method; accuracy may be improved by the use of angle-correction formulas.

2. Cardiac catheterization

a. The **amplitude of the v waves** on hemodynamic tracings (which are a reflection of LA filling from the pulmonary veins during ventricular systole) can provide clues to the severity of MR, particularly in acute MR.

(1) Amplitudes of v wave more than two to three times mean LA pressure suggest severe MR. However, in slowly developing MR, an abnormal v wave may not be seen. The v waves are also diminished by afterload reduction. **The absence of v waves does not exclude severe MR.**

(2) Other conditions that may produce prominent v waves are LV dysfunction with a dilated noncompliant left atrium, postinfarction VSD, and other situations in which there is increased pulmonary blood flow.

b. Left ventriculography allows the visual assessment of the severity of MR. It is affected by multiple factors such as the adequacy of the contrast injection to fill the ventricle, the placement of the catheter, and ventricular arrhythmia during injection. The grading system is as follows:

1. **1+ (mild):** clears with each beat; entire left atrium is never opacified.
2. **2+ (moderate):** does not clear with a single beat; may faintly opacify the entire left atrium.
3. **3+ (moderate to severe):** fills entire left atrium over 2 or 3 beats; complete opacification of the left atrium, equal in intensity to the left ventricle.
4. **4+ (severe):** complete opacification of the left atrium in 1 beat; contrast material refluxes into the pulmonary veins.

c. Coronary angiography is useful to detect **concomitant coronary artery disease** (CAD) in these patients. Those being considered for surgery to correct MR undergo coronary angiography, even in the absence of symptoms, if they are older than 50 years or have multiple risk factors.

E. Therapy. An understanding of the pathophysiologic mechanism of MR is essential to management.

1. Acute MR

a. **Medical therapy.** If there is adequate mean arterial pressure, pharmacologic therapy with **afterload reducing agents** may reduce the acute MR. Intravenous nitroprusside and nitroglycerin may reduce pulmonary pressures and maximize forward flow. If surgery is not immediately indicated a switch to oral agents may be made. Angiotensin-converting enzyme (ACE) inhibitors

(ACE-I) and direct-acting vasodilators (such as hydralazine) help maximize forward output and reduce regurgitant fraction.

- b. **Percutaneous therapy.** The large sudden volume overload on an left ventricle that is not dilated or hypertrophied causes symptoms of pulmonary congestion and even cardiogenic shock. For such patients with acute hemodynamically significant MR, especially from postinfarction PM rupture, placement of an intraaortic balloon pump (IABP) may serve as a temporary stabilizing measure until surgical repair can be undertaken.
- c. **Surgical therapy.** Patients with acute, severe MR usually require urgent surgical intervention.

2 Chronic MR

- a. Choosing the appropriate therapy (see Table 16.4 for a summary of the current ACC/AHA guidelines)
 - (1) Most patients who have **moderately severe to severe MR** and are **symptomatic** should be considered for elective surgical treatment. Decisions need to be individualized based on the age of the patient, the likelihood of valve repair, comorbidities, LV function, and the likelihood that surgical intervention will improve symptoms and/or survival. Generally, **intervention for symptoms is indicated for severe MR if the cause of the MR is primary to the valve** (i.e., prolapse, rheumatic, or congenital in origin). When the **valve lesion is secondary to ventricular dysfunction**, either from ischemic heart disease or from dilated cardiomyopathy, **aggressive medical management of heart failure** (see subsequent text) is indicated first.
 - (2) In **severe MR due to dilated cardiomyopathy associated with severe symptoms** and refractory to medical management and cardiac resynchronization therapy (CRT) where indicated, mitral valve repair may lead to symptomatic improvement, but a survival benefit has not yet been demonstrated.
 - (3) Management of patients with **minimal or no symptoms but severe MR** is more complex. **The key is to identify patients before contractile dysfunction of the left ventricle becomes irreversible.** Watchful waiting until serious symptoms develop carries a risk for the development of severe LV dysfunction and a poor prognosis. The feasibility of mitral valve repair with improved postoperative survival and EF (see later) has been another incentive in the push for earlier surgical intervention. If the valve repair is not feasible, one may choose to wait longer before proceeding to surgical treatment. The 2006 valve guidelines **lowered the threshold to intervene in asymptomatic patients with repairable valves** when repair is performed in an experienced center where the likelihood of repair exceeds 90% (Table 16.4).
- b. **Timing of surgery.** A variety of clinical, echocardiographic, and invasively derived values appear to be predictive of the development of postoperative LV dysfunction, decompensated heart failure, and death among patients with significant but asymptomatic MR. The timing of mitral valve surgery is a **decision that must be individualized** and depends on several variables, including clinical signs and symptoms, echocardiographic findings, catheterization data, hemodynamic data, operative risk, and reparability of the mitral valve. Generally, the variables to be considered in patients whose MR is asymptomatic are (a) LV size and function; (b) exercise capacity and LV size and function at peak exercise; (c) reparability of the valve; (d) severity of MR, including the presence of flail leaflet; (e) pulmonary artery pressures; (f) atrial fibrillation; and (g) age and other comorbidities.

TABLE 16.4 Indications for Mitral Valve Surgery in Mitral Regurgitation**Class I**

- (a) MV surgery is recommended for the symptomatic patient with acute severe MR
- (b) MV surgery is of benefit for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction < 0.30) and/or end-systolic dimension > 55 mm
- (c) MV surgery is of benefit for asymptomatic patients with chronic severe MR and mild to moderate LV dysfunction, ejection fraction 0.30 – 0.60 , and/or end-systolic dimension ≥ 40 mm
- (d) MV repair is indicated over MV replacement in most patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in MV repair

Class IIa

- (a) MV repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR with preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom the likelihood of successful repair without residual MR is $> 90\%$
- (b) MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new-onset atrial fibrillation.
- (c) MV surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and pulmonary hypertension (pulmonary artery, systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise)
- (d) MV surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction (ejection fraction < 0.30 and/or end-systolic dimension > 55 mm) in whom MV repair is highly likely

Class IIb

MV repair may be considered for patients with chronic severe secondary MR due to severe LV dysfunction (ejection fraction < 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing

Class III

- (a) MV surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom significant doubt about the feasibility of repair exists
- (b) Isolated MV surgery is not indicated for patients with mild or moderate MR

MV, mitral valve; MR, mitral regurgitation; NYHA, New York Heart Association; LV, left ventricular.

Adapted from 2006 Valve Disease ACC/AHA Valve Disease Guidelines.

- (1) LV size and function. As noted previously, contractile impairment is often occult in severe MR when conventional indices of LV function are used. Elastance measured at the time of cardiac catheterization is the best load-independent measure of true contractile function in MR. However, as it requires the construction of a series of pressure–volume loops for its calculation, it is rarely performed outside research laboratories. Fortunately, conventional indices of LV size and function do

provide useful information in MR. Newer noninvasive techniques, such as two-dimensional (2D) strain imaging, are of interest because of their ability to detect subtle changes in LV function that precede reductions in EF. **In severe primary MR with preserved contractile function, left ventricular ejection fraction (LVEF) should be in the high-normal range. Studies have indicated that once the LVEF is < 60%, the likelihood of impaired survival and permanent LV dysfunction postoperatively is high.** Therefore, consideration should be given to surgical intervention before the LVEF drops to below 60%. Increased LV size and volume in end systole (more load-independent than end diastole) is also an indicator of increased likelihood of impaired survival and LV dysfunction postoperatively. When **LV end-systolic diameter is > 4.0 cm, surgical intervention should be considered.**

- (2) We have found that **exercise echocardiography** is very helpful in determining the likelihood of latent LV contractile dysfunction. **The ability of the left ventricle to cope with exercise is an indication of its contractile reserve.** In addition, **poor functional capacity** may indicate an adaptive response to MR (the patient was not truly asymptomatic) and may influence the decision to proceed with surgical treatment. We have found that a **failure to increase LVEF, or for end-systolic volume to decrease with stress, is predictive of postoperative LV dysfunction** and is a superior predictor of this eventuality than resting LVEF. In patients with severe asymptomatic MR, we perform stress echocardiography at 6-month intervals and recommend mitral valve surgery once end-systolic volume fails to decrease significantly at peak exercise or if LVEF fails to increase. This is particularly helpful in patients who wish to postpone surgical intervention as long as possible.
- (3) The **feasibility of repair** depends on the cause of MR. This can be determined during the preoperative evaluation by echocardiography. **Repair in an experienced center is usually likely in MVP unless chordae to both leaflets are severed, severe damage from endocarditis has occurred, or there is extensive leaflet calcification.** Repair is usually feasible for a cleft valve and in less extreme forms of endocarditis such as leaflet perforation without chordal disruption, as well as in many cases of secondary MR (ischemic or dilated cardiomyopathy). Repair is more difficult to achieve in rheumatic involvement and when the valve leaflets or chordae are severely disrupted from any cause. **The threshold to intervene surgically is lower if repair appears feasible because of the lower surgical and long-term mortality and morbidity associated with repair compared with replacement.**
- (4) The more severe the MR, the greater the volume load on the left ventricle usually, and the more likely that LV dysfunction will develop. One caveat here is that MR is not always holosystolic. Occasionally, apparently severe MR is seen without evidence of significant LV enlargement because the MR is occurring only in the latter part of systole.

The threshold to intervene surgically is lower as MR severity increases. In situations where MR severity is in doubt, a TEE should be performed and the quantitative assessment used as described previously. A flail leaflet usually (but not always) implies severe MR. A retrospective study suggested that earlier surgical intervention was associated with better long-term survival in patients with a flail leaflet, even if the condition was asymptomatic, with flail being considered a surrogate for severe MR. More recent quantitative studies suggest that once ROA is $\geq 0.4 \text{ cm}^2$, survival is better in those treated surgically, even in the absence of symptoms.

- (5) Pulmonary pressures > 50 mm Hg at rest or > 60 mm Hg at peak exercise in the absence of another likely cause are an indication of severe MR and impaired survival and these **are considered ACC/AHA class IIa indications for surgical intervention**. These can be assessed noninvasively from the tricuspid regurgitant velocity at stress echocardiography.
- (6) The occurrence of **atrial fibrillation** or flutter in the setting of severe MR is considered an indication (IIa) for surgical intervention. A concomitant maze or more usually now a modified maze procedure (pulmonary vein and great vein isolation) may be performed with mitral valve repair, especially if atrial fibrillation has become persistent or frequent.
- (7) Age and other comorbidities. Patients > 75 years, those with concomitant CAD, or those with renal dysfunction have worse outcomes after surgical treatment. Patients with ischemic MR have a worse prognosis than those with regurgitation from other causes.

c. Medical therapy

- (1) The role of medical therapy for **asymptomatic, chronic MR caused by primary valve disease** is not well established. There is no evidence that pharmacologic agents delay progression of the disease or prevent ventricular dysfunction. Patients with severe MR should be evaluated semiannually with echocardiography and stress echocardiography, if indicated. Patients with moderate MR should be evaluated annually.
 - (a) The success of afterload reducers in acute MR has led to trials of vasodilators, such as **ACE-I and hydralazine**, in chronic MR. However, existing small trials have been largely negative. As a result, the ACC/AHA and European Society of Cardiology guidelines recommend against the use of pharmacological vasodilatation in chronic MR with preserved EF, although this is not necessarily reflected in common practice.
 - (b) Sympathetic overstimulation appears to be a key element of progression to LV failure in MR, and there is limited evidence for the experimental use of β -blockers in MR but no clinical evidence of utility of postponement of surgical intervention.
 - (c) MR secondary to LV dysfunction is managed with standard heart failure therapy, including ACE-I and β -blockers.
 - (d) Diuretics and nitrates have a role in the management of pulmonary congestion.
 - (e) Ventricular rate-controlling agents and antiarrhythmics are used for atrial fibrillation. **Digitalis and β -blockers** are the mainstay of therapy for rate control. In severe MR with atrial fibrillation, maintenance of sinus rhythm is unlikely if the regurgitation remains uncorrected.
- (2) **In accordance with recent AHA guidelines**, endocarditis prophylaxis is not routinely indicated in patients with MR. These new guidelines recommend that prophylaxis be used only in patients with underlying cardiac conditions associated with the highest adverse outcome from infective endocarditis, including prosthetic heart valves or prior repair surgery, previous infective endocarditis, certain classes of congenital heart disease, and in valvulopathy occurring post cardiac transplantation.

d. Surgical therapy

- (1) Mitral valve replacement with transection of the subvalvular apparatus was once the only approach used in the surgical management of MR. Postoperative reduction of LV function and decompensated heart failure were common sequelae. Chordal preservation by leaving the subvalvular structures intact has been shown to reduce LV volumes and wall stress postoperatively and is now the technique of choice.

- (2) The increasing success of **mitral valve repair** has greatly reduced the morbidity and mortality associated with severe MR. Mitral valve repair almost always involves placement of an undersized annuloplasty ring, which reduces annular diameter, improves leaflet coaptation, and significantly decreases MR. Additional components may include a pericardial patch at the site of leaflet perforation, chordal shortening or transposition, leaflet resection, and sliding valvuloplasty of the posterior leaflet to reposition the coaptation line. Artificial chordae are increasingly used in the repair of anterior leaflet prolapse.
- (3) Although no randomized trials have compared repair with replacement, **comparative data suggest better postoperative LV function and survival with repair** (which in part reflects the selection of patients who are able to undergo repair). Long-term risk of thromboembolism and endocarditis is reduced with repair versus replacement, and the need for reoperation is similar. Excellent 20-year outcomes following repair have been reported from multiple large volume centers, with the estimated risk of reoperation approximating 10%.
- (4) **Minimally invasive** video-assisted approaches employing hemi-lower sternotomy and right thoracotomy incisions may be options in experienced centers and selected patients. In the latter, cardiopulmonary bypass is usually achieved via femoral artery and vein cannulation. These approaches have the benefit of smaller incisions, resulting in more rapid postoperative recovery but require considerable expertise. Introduction of robotic surgical instrumentation and high-definition three-dimensional (3D) imaging allows mitral valve repair through portlike incisions, with further reduction in procedural invasiveness. **Robotically assisted valve repair** has shown good results in a few centers, although there are currently no data for superior outcomes. Complex surgeries, particularly if they require concomitant coronary artery bypass grafting (CABG) or multivalvular repair, are likely better handled with a standard operative approach at this point. These techniques may enjoy broader application in the future.
- (5) **Mitral valve replacement** is indicated when repair is not technically possible. The choice of **mechanical or bioprosthetic** valve replacement depends on weighing the risk of chronic anticoagulation required with mechanical valves, against the reduced longevity of the bioprosthetic valves. Structural degeneration of bioprosthetic mitral valves typically affects 20% to 40% patients at 10 years and over 60% at 15 years.
- (6) Intraoperative echocardiography helps in the **assessment of complications** of valve repair or replacement.
 - (a) Residual MR is the most common problem after a pump run. If further repair is feasible, a second pump run should be considered to correct residual MR (if 1+ or greater). If further repair is not possible, valve replacement may be needed. A second pump run does not appear to increase in-hospital mortality.
 - (b) **Dynamic LV outflow obstruction** is an important potential complication of mitral valve repair. This is now uncommon in experienced centers. It is caused by anterior displacement of mitral leaflet coaptation point when the posterior leaflet is redundant (typically > 1.5 cm in height). The result is systolic motion of the mitral leaflet into the outflow tract, creating a pressure gradient across the outflow tract and the development of MR. This may be apparent immediately after surgery in the operating room, with intraoperative echo or later in the course. It is exacerbated by increased inotropy and small LV size. Many instances resolve with cessation of the use of

sympathomimetic agents and volume repletion. In the operating room, if these efforts fail to correct the condition, more surgery to reduce the height of the posterior mitral leaflet (sliding annuloplasty) or, rarely, mitral valve replacement may be necessary. In the post-operative patient, volume repletion and judicious use of β -blockade are often all that is necessary, although occasionally surgical revision of the repair is needed. The development of a new apical systolic murmur in the patient who has undergone mitral valve repair should prompt an echocardiogram to exclude this complication.

e. Postsurgical follow-up care

- (1) Baseline echocardiography should be performed postoperatively. This is ideally scheduled 4 to 6 weeks after the operation, but for the sake of convenience it is often done before hospital discharge (within 3 to 4 days).
- (2) MR can recur because of failure of the repair or because of progression of the disease that caused MR. Patients should undergo clinical evaluations at least once a year. **Yearly echocardiography** after the operation to assess for MR and LV function is reasonable.

f. Resynchronization therapy. LV wall motion abnormalities are often the major pathology in secondary (functional) MR, and CRT has demonstrated symptomatic benefit in carefully selected patients.

g. Percutaneous mitral valve repair. Percutaneous mitral valve repair is a developing catheter-based treatment option in which improved coaptation of the mitral leaflets is attempted using an implantable device. Current techniques emulate the existing surgical procedures, with the devices currently under investigation being classified into two functional approaches.

- (1) A **clip** can be used to approximate the center of the mitral valve leaflets, thus giving a double-orifice valve in an approach that models the surgical Alfieri edge-to-edge repair. To date, this is the best studied percutaneous option, with the Endovascular Valve Edge-to-Edge Repair Study II recently reporting the 12-month results of 279 patients with 3 to 4+ MR randomized to MitraClip (Abbott Vascular, Menlo Park, CA, USA) versus surgical mitral valve repair/replacement. The primary composite end point for efficacy was freedom from death, from mitral valve surgery, and from 3 or 4+ MR. About 55% of subjects in the percutaneous repair group met the end point at 1 year compared with 73% in the surgery group. All-cause mortality was equivalent in the percutaneous and surgical groups. There were significantly fewer adverse events in the percutaneous group, although significance was lost when blood transfusion was excluded as a complication. Implantation of the MitraClip is currently performed in the United States as part of a continued access registry.
- (2) A **flexible ring** can be deployed and tightened in the coronary sinus (CS) in order to effectively reduce the mitral annulus area. Concerns regarding this procedure include the variable relationship between the CS and mitral annulus, as well as the proximity to the circumflex artery. Devices under investigation include two stents deployed into the CS, with the connecting coil bridge being tightened over time called the Monarc (Edwards Lifesciences, Irvine, CA, USA); a fixed length, double-anchor CS device called the Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA, USA); and a CS anchor that is attached to the interatrial septum via a cord under tension called the Percutaneous Septal Shortening System (Ample Medical, Foster City, CA, USA).

The clip may be more appropriate for repair of MVP, whereas annular remodeling is felt to be better suited for the repair of functional regurgitation.

III. ISCHEMIC MR (IMR)

A. Clinical presentation. IMR may present either acutely in the setting of active ischemia or infarction or chronically with long-standing CAD. Among patients with CAD, the presence of MR portends a worse prognosis. Acute severe IMR presents with cardiogenic shock and hemodynamic instability, with symptoms and signs consistent with those previously described for acute MR. The clinical presentation of chronic IMR also parallels that of other etiologies of chronic MR; in addition, a history of known CAD or cardiovascular risk factors should be sought.

B. Etiology and pathology

1. Ischemia or infarction may give rise to one or more of the following mechanisms of IMR. Those common in the acute setting include the following:
 - a. PM rupture or chordal avulsion;
 - b. altered LV geometry, causing PM displacement; and
 - c. elongation of the infarcted PM and exaggerated contraction of the noninfarcted PM.
2. Mechanisms common in the chronic IMR setting include
 - a. PM necrosis causing leaflet tethering and poor coaptation;
 - b. decreased mitral valve closing forces because of LV systolic dysfunction; and
 - c. LV cavity dilation causing mitral valve annular dilation.
3. The anterolateral PM receives its blood supply from the left anterior descending and circumflex circulations; the posteromedial PM is supplied by the right coronary or left circumflex artery depending on the coronary dominance.
4. Of note, acute IMR is more frequently a result of geometric changes due to regional LV dysfunction (especially of the inferolateral wall) that induce leaflet tethering and prolapse, rather than ischemia of the PM itself.

C. Laboratory examination and diagnostic testing

1. **Echocardiography.** The most important determinations are the assessment of valvular anatomy, quantification of regurgitation, and evaluation of LV structure and function. Echocardiography can often reveal the mechanism of IMR by evaluating for PM rupture, leaflet restriction, mitral valve tethering, and relevant regional wall motion abnormalities. As previously described, the degree of regurgitation is quantified using color flow and Doppler techniques. Urgent trans-thoracic echocardiography and/or TEE is the investigation of choice in a patient with acute pulmonary edema where IMR is being considered as an etiology.
2. **Electrocardiogram (ECG).** In acute IMR, ECG is key in evaluating for the presence of active ischemia or infarction. As described above, branches from the left or right coronary systems can supply the PMs. However, it is in the setting of inferior or inferolateral MIs that acute IMR is most commonly seen. In chronic IMR, LA abnormalities, atrial fibrillation, and nonspecific ST-T changes may be seen.
3. **Chest radiography.** In acute IMR, findings of pulmonary edema may be present. Cardiomegaly with LA and LV enlargement may be seen in chronic IMR.
4. **Cardiac catheterization.** Evaluation of the patient with IMR will include angiography to assess the location, extent, and revascularization options of the CAD. In some cases, invasive hemodynamics may provide useful additional data regarding MR severity.

D. Therapy.

1. Intravenous afterload reduction with nitroprusside and nitroglycerin +/- IABP insertion is often required when managing cardiogenic shock secondary to acute IMR. This scenario is associated with a **very poor prognosis**, and surgical intervention with coronary artery bypass and valve repair or replacement is usually the only hope for survival.
2. The medical management of chronic IMR with preserved EF remains controversial, as described above. If LV dysfunction is present, the use of a heart failure medical regimen is essential.

3. Patients with significant IMR will likely require surgery for revascularization and valve repair or replacement. However, studies to date **have not demonstrated any long-term benefit from the addition of valvular surgery to CABG** in this setting. The success rate and durability of valve repair in IMR are significantly lower than those of degenerative mitral valve disease.

IV. MITRAL VALVE PROLAPSE

A. Clinical presentation. Prolapse exists when either or both of the mitral leaflets protrude > 2 mm beyond the annulus into the left atrium during systole, and the coaptation point of the leaflets lies superior to the plane of the annulus. A wide spectrum of pathologic changes and clinical symptoms have been observed, from mild degrees of prolapse diagnosed with echocardiography only to clinically evident severe MR. MVP is the most common cause of MR in the United States. **It affects approximately 2% of the population. Recent studies have suggested an equal prevalence among males and females. Males and older patients (age > 45 years) are disproportionately more likely to require surgical intervention** and to develop other major complications such as endocarditis.

1. Signs and symptoms

- a. Most patients with MVP have **no symptoms**, and the diagnosis is made by means of routine examination or echocardiography performed for other indications.
- b. Although in the past many symptoms were attributed to MVP, including chest pain, panic attacks, and autonomic instability, more recent studies suggest that these occur no more frequently in patients with MVP than in control populations. Most symptoms associated with adverse prognostic implications occur when significant MR is present.
- c. Arrhythmias are more common with MVP, even in the absence of MR. These include **supraventricular tachyarrhythmias, ventricular tachyarrhythmias, and bradyarrhythmias**. Sudden cardiac death is a rare complication in MVP, occurring in < 2% patients over long-term follow-up. It is more common in the setting of severe MR and/or flail valve leaflet and is likely due to ventricular arrhythmias.
- d. Transient ischemic attack or stroke has been reported in MVP. The most recent studies in this area suggest no excess risk of cerebrovascular events among young patients with MVP.
- e. When prolapse causes MR, symptoms referable to the valvular insufficiency may be present.

2. Physical findings

- a. **Inspection.** There is a higher than expected incidence of **pectus excavatum** among patients with mitral valve. Straight back and scoliosis are also found. Patients often have low body weight and relative hypotension.
- b. The main **auscultatory** findings are shown in Figure 16.4. The **midsystolic click** is the classic finding in prolapse. A systolic murmur is heard if MR is present.
- c. Dynamic changes are elicited by **conditions that decrease LV size** (decreased venous return, increased contractility, or decreased systemic volume), which lead to earlier occurrence of prolapse, an earlier click, and increased duration of the murmur. These conditions include standing, the Valsalva maneuver, dehydration, and exposure to amyl nitrite.
- d. Maneuvers that **increase LV size** by increasing venous return, decreasing contractility, or increasing systemic volume move the click and murmur later into systole. Examples include squatting and infusion of phenylephrine. The presence of a **click that responds to provocative maneuvers is sufficient**

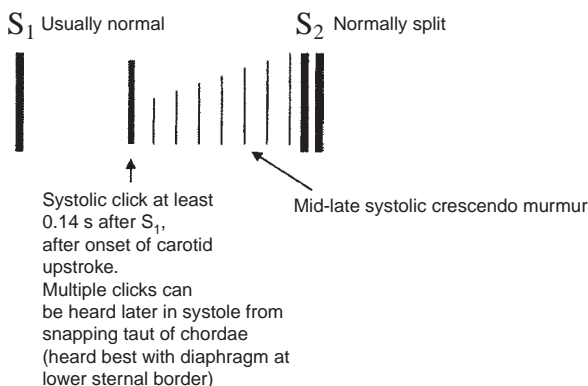


FIGURE 16.4 Auscultatory findings in mitral valve prolapse.

for the diagnosis of prolapse, even if an echocardiogram is not diagnostic (see [Section III.D.1](#)).

- e. The **intensity of the murmur typically decreases with conditions that result in a later click and murmur**. An exception is exposure to amyl nitrite, which also reduces LV systolic pressure and the gradient that drives regurgitant flow. As such, the murmur is of lower intensity, although it occurs earlier in systole.
 - f. Aortic and pulmonic ejection sounds can produce systolic clicks. These occur earlier in systole than the click of mitral prolapse and may be differentiated on the basis of timing in conjunction with the carotid upstroke. Other causes of midsystolic clicks include septal and free wall aneurysms and mobile tumors such as myxoma. Clicks produced by these conditions do not change with maneuvers that alter LV volume.
- B. Etiology and pathology.** Prolapse may exist as a result of valvular abnormalities, deemed primary prolapse, or occur in the setting of normal leaflets (secondary prolapse).

1. Primary prolapse results from **myxomatous proliferation of the leaflets.**

Myxomatous mitral valve disease describes thickening of the leaflets and chordae tendineae due to abnormal accumulation of **mucopolysaccharides**, with prominence of the spongiosa layer of the leaflets. Impaired tensile strength is more marked in the chordae than in the leaflets. Chordal elongation results in prolapse and loss of leaflet coaptation and may cause MR. **Thickening of the leaflets ≥ 5 mm is considered “classic” MVP** and is associated with greater future complications.

- a. Within the pathological spectrum of myxomatous mitral valve disease, there are two subtypes of diseases. **Barlow disease** is seen in younger patients, shows greater annular dilation, and has more marked leaflet redundancy and prolapse that may involve multiple segments. Conversely, **fibroelastic deficiency** occurs in older patients, is typically confined to the posterior middle scallop (P₂), and is associated with thinning and rupture of chordae.
- b. Primary prolapse appears to have a genetic predisposition. There is a higher prevalence of MVP among family members of those affected, and an **autosomal dominant** mode of inheritance with variable penetrance has been postulated. Recent linkage studies suggest a site on chromosome 16 in some families

with MVP. In addition, MVP is seen as part of disorders with more generalized abnormalities of the connective tissue, such as Marfan syndrome, Ehlers-Danlos syndrome, pseudoxanthoma elasticum, and myotonic dystrophy.

- c. Most **complications** of prolapse, particularly severe MR, are associated with primary prolapse. Men in their third decade of life represent the most common demographic group with such a presentation.
 2. In **secondary prolapse**, there is relatively **normal valvular structure**. A disproportion between leaflet size and LV cavity size produces mechanical forces that may lead to leaflet prolapse. This form of prolapse particularly affects **younger women**. It may also occur with atrial septal defect, hyperthyroidism, emphysema, and hypertrophic cardiomyopathy. Normalization of the relative disproportion between leaflet size and cavity size often occurs with ageing among women, so the incidence decreases with age. **Secondary prolapse is usually of little clinical significance and is not usually associated with significant MR.**
- C. Laboratory examination and diagnostic testing**
1. **Echocardiography.** M-mode demonstrates late or holosystolic bowing of the mitral valve leaflet 3 mm or more below the C–D line. In 2D echocardiography, prolapse is defined as **>2-mm displacement of one or both mitral leaflets into the left atrium during systole in the parasternal or apical long-axis views**. Caution must be used in making the diagnosis with the apical four-chamber view because normal valve leaflets may appear to prolapse in this view owing to the saddle shape of the mitral annulus. With primary causes of prolapse, increased leaflet thickness (≥ 5 mm) and redundant leaflets and chordae are seen. Doppler echocardiography is used to assess the presence and severity of MR. Annual echocardiography is advised for those patients with moderate to severe MR.
 2. **Electrocardiogram.** If there is severe MR, the findings described earlier are present. Otherwise, the ECG usually is normal or has nonspecific ST-T changes.
 3. **Chest radiography.** Pectus excavatum or scoliosis can be present in some cases. If severe MR is present, the typical findings described earlier are seen. Otherwise, the **chest radiograph is usually normal.**
- D. Therapy.** For most patients, MVP carries a benign prognosis, and **periodic clinical follow-up examinations and reassurance** are all that is needed.
1. Endocarditis prophylaxis is not routinely indicated in patients with MVP.
 2. Approximately 10% to 15% of patients, particularly those with redundant and thickened leaflets, eventually develop progressive MR. Chordal rupture is a contributing factor among these patients. **Management of MR** is outlined in **Section II.E**. Patients with evidence of primary MVP should avoid situations that might increase the stress on the chordae, such as sudden heavy lifting.
 3. For patients with a history of **transient ischemic attacks, antiplatelet therapy with aspirin** (80 to 325 mg/d) is indicated. The ACC/AHA guidelines also recommend aspirin for poststroke patients with MVP who have no evidence of MR, atrial fibrillation, LA thrombus, or echocardiographic evidence of thickening (≥ 5 mm) or redundancy of the valve leaflets. However, long-term **anticoagulation therapy with warfarin** is recommended if any of these higher risk features are present, and in MVP patients with recurrent transient ischemic attacks while taking aspirin (international normalized ratio [INR]: 2.0 to 3.0). Aspirin is sufficient for patients with MVP and atrial fibrillation who are < 65 years, have no MR, and have no history of stroke, hypertension, or heart failure.
 4. Patients who experience palpitations should be advised to abstain from caffeine, alcohol, and tobacco use. **β -Blockers** are useful in the management of premature atrial or ventricular contractions and often alleviate symptoms. **Ambulatory electrocardiographic monitoring** is recommended for persistent palpitations. Ventricular tachycardia is an indication for **electrophysiologic testing** to assess the risk of sudden death and the possible need for **implantation of a defibrillator device.**

V. MITRAL STENOSIS. Although declining in incidence in the United States, rheumatic disease remains the predominant cause of MS. Other etiologic factors are listed in Table 16.5. In general, once symptoms begin to develop, there follows a period of about 10 years before they become debilitating. Once significant limiting symptoms develop, the 10-year survival rate is < 15%.

A. Clinical presentation

1. Signs and symptoms

- a. There is often a **long asymptomatic course**, consisting of a couple of decades.
- b. When symptoms do develop, **dyspnea** is common. Predominant symptoms are exertional dyspnea initially, followed by paroxysmal nocturnal dyspnea and orthopnea, which reflect elevated pulmonary venous pressure.
- c. Precipitating factors, such as exercise, emotional stress, pregnancy, infection, or atrial fibrillation with a rapid ventricular response, can produce or dramatically worsen symptoms by generating increased transvalvular gradients and LA pressure. **Atrial fibrillation with rapid ventricular response is a classic exacerbating factor** and may produce pulmonary edema, even in those with mild MS. The LA dilation is a predisposing factor for the development of atrial fibrillation.
- d. Hemoptysis can occur and likely represents rupture of small bronchial veins from elevated LA pressure.
- e. Hoarseness occurs when the dilated left atrium impinges on the recurrent laryngeal nerve (Ortner syndrome).
- f. LA dilation and stasis, particularly in the context of atrial fibrillation (persistent or paroxysmal), may cause thrombus formation and embolic events. **Cerebrovascular events, coronary embolization, and renal emboli and infarction** are all possible sequelae. The malformed valve is predisposed to the development of **endocarditis**.
- g. Fatigue is common because of reduced cardiac output.
- h. With long-standing MS and elevated pulmonary pressure, symptoms of **RV failure** may develop.
- i. Patients with elevated pulmonary pressures may have **angina-like chest pain**, as a reflection of increased RV oxygen demand.

TABLE 16.5 Causes of Mitral Stenosis

Rheumatic: most common cause

Congenital

Parachute mitral valve: single papillary muscle to which chordae to both leaflets attach; results in mitral stenosis or mitral regurgitation

Supravalvular mitral ring

Systemic diseases: can cause valvular fibrosis

Carcinoid

Systemic lupus erythematosus

Rheumatoid arthritis

Mucopolysaccharidosis

Healed endocarditis

Prior anorectic drug use

Severe mitral annular calcification

2. Physical findings

a. **Inspection and palpation.** Patients may have a **malar facial flush**. The jugular venous pulse can demonstrate a **prominent a wave** if there is elevated pulmonary vascular resistance and the patient is still in sinus rhythm. **Jugular venous pressure is elevated with RV failure**. In advanced cases with low cardiac output, **peripheral cyanosis** occurs. The **carotid upstrokes are usually normal** but are of low amplitude if there is diminished cardiac output. The apex beat is not displaced and the impulse can have a tapping quality due to a palpable first heart sound. An apical diastolic **thrill** may be felt in the lateral decubitus position and has a quality that simulates a purring cat. If there is pulmonary hypertension, a **parasternal RV lift with a palpable P_2** is present.

b. **Auscultation.** The main auscultatory findings are shown in Figure 16.5.

- (1) The **opening snap** is the most characteristic auscultatory hallmark of MS. However, as the mitral valve becomes more calcified and immobile, the opening snap may be lost (just as S_1 becomes softer).
- (2) The **murmur** of MS is typically a low-pitched rumbling mid-diastolic murmur, heard best with the bell of the stethoscope with the patient in the left lateral decubitus position. Presystolic accentuation can be present whether or not the patient is in sinus rhythm (exact mechanism is unknown). Auscultation after a **brief period of exercise may accentuate the murmur** of MS as the increased output and heart rate increase the transvalvular gradient. The length of the murmur correlates better with the severity of MS than the loudness. **The longer the murmur and the shorter the time interval from S_2 to the opening snap**, the more severe the MS.
- (3) Concomitant **conditions that result in decreased flow across the valve**, such as CHF, pulmonary hypertension, and aortic stenosis, may **reduce the diastolic murmur**. The presence of a loud S_1 may be the only clue to the presence of MS in these cases, particularly if pulmonary hypertension exists.
- (4) Auscultation of the lungs may reveal fine inspiratory crackles. However, it is remarkable that some patients with severe MS have clear lung fields, possibly due to lymphatic hyperfunction clearing the transudated alveolar fluid that would be expected from the elevated LA pressure.

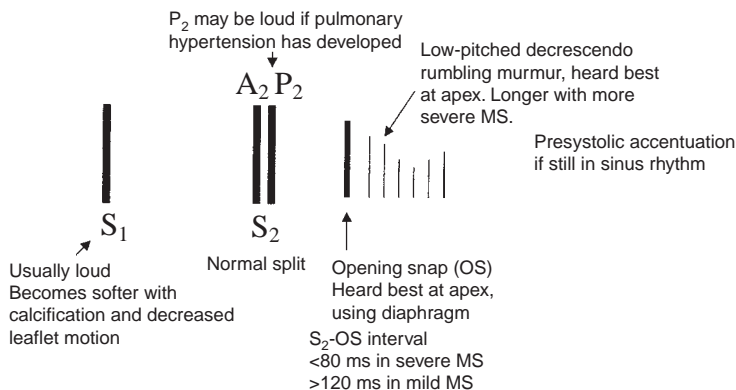


FIGURE 16.5 Auscultatory findings in mitral stenosis.

- (5) Other **conditions that mimic** the clinical presentation of MS include LA myxoma and cor triatriatum. The tumor plop of myxoma may be mistaken for an opening snap, and tumor obstruction of the valve leads to a diastolic murmur. However, in this condition, the physical findings will vary with changes in position and from examination to examination. Other conditions in which a diastolic rumble may be present include atrial septal defect or VSD, the Austin-Flint murmur of aortic regurgitation (the murmur lessens with decreased afterload and is preceded by an S_3 , and the S_1 is normal), and tricuspid stenosis (the murmur is heard at the left sternal border and typically increases with inspiration, known as Carvallo's sign).

B. Etiology (Table 16.5)

- In **rheumatic MS**, up to 50% of patients are not aware of a history of rheumatic fever. Rheumatic fever is now rare in developed nations, although it is unclear whether this is due to improvements in living conditions or a change in the virulence or immunogenicity of *Streptococcus pyogenes*.
 - In **acute** rheumatic fever, MR often predominates. Stenosis usually develops anywhere from 2 to 20 years later, and symptoms may not develop for many years thereafter. Although the incidence of rheumatic fever is roughly equal between men and women, rheumatic MS develops two to three times more frequently in women.
 - Thickening of leaflets with **fibrous obliteration** is a characteristic finding. Commissural and chordal fusion and chordal shortening contribute to the development of stenosis. Calcium deposition occurs on leaflets, chordae, and annulus, further restricting valvular function. These changes collectively produce a funnel-shaped mitral valve with a fish-mouth orifice.
- Nonrheumatic MS causes include congenital malformation, extensive annular calcification in the elderly, radiation heart disease, and restrictive mitral valve repair for MR.

C. Pathophysiology

- The normal area of the mitral orifice is 4 to 6 cm^2 . When the valve area is $< 2 \text{ cm}^2$, a **pressure gradient between the left atrium and the left ventricle in diastole occurs**. As orifice area declines, both the transmitral pressure gradient and the LA pressure increase, but these are also affected by the flow through the valve. **Although the transmitral pressure is a useful indicator of MS severity, it is critically affected by the cardiac output at any moment. The cross-sectional area of the mitral valve orifice is, for the most part, independent of flow considerations and thus is a more robust measure of the severity of MS.**

Typical findings indicative of the **severity of stenosis** as defined by the American Society of Echocardiography and endorsed by the recent ACC/AHA valve disease guidelines are as follows:

- Severe** stenosis is associated with a **mean** transvalvular gradient **$> 10 \text{ mm Hg}$** , PA pressures **$> 50 \text{ mm Hg}$** , and a valve area **$< 1.0 \text{ cm}^2$** .
- Moderate** stenosis is associated with a **mean** transvalvular gradient of **5 to 10 mm Hg**, PA pressures of 30 to 50 mm Hg, and a valve area of **1.0 to 1.5 cm^2** .
- Mild** stenosis is associated with a **mean** transvalvular gradient of **$< 5 \text{ mm Hg}$** , PA pressures **$< 30 \text{ mm Hg}$** , and a valve area **$> 1.5 \text{ cm}^2$** .

The severity of the stenosis needs to be assessed in terms of not only the valve area but also symptomatology and exercise capacity. Mixed MS and MR is often associated with greater symptomatic impairment than might be predicted from the severity of either lesion alone.

- The **increased LA pressure is transmitted to the pulmonary vasculature**, resulting in symptoms of pulmonary congestion. The passive increase in pulmonary venous pressure may elevate pulmonary vascular resistance (reactive pulmonary hypertension). This condition is usually reversible if the stenosis is

relieved. However, in long-standing, severe MS, obliterative changes in pulmonary vasculature may occur. Severe pulmonary hypertension can in turn lead to right-heart failure.

3. Up to 30% of patients have a **depressed LVEF**. This appears to result from decreased preload (decreased inflow into the left ventricle) or a rheumatic myocarditis. The former will normalize after a corrective mitral valve procedure, the latter will not.
4. In severe MS, there may be sufficiently low cardiac output to cause **symptoms of poor perfusion**. Chronically depressed cardiac output causes a reflex increase in systemic vascular resistance and increased afterload. This may further diminish LV performance.

D. Laboratory examination and diagnostic testing

1. Echocardiography has several critical roles in the evaluation of MS (all endorsed by ACC/AHA recommendations): initial diagnosis, determination of severity, evaluation of suitability for percutaneous balloon mitral valvuloplasty, and identification of concomitant valve lesions.
 - a. M-mode findings include dense echoes on the mitral valve and decreased excursion of the mitral valve. **Poor leaflet separation in diastole, anterior motion of the posterior leaflet, and decreased E–F slope on the anterior leaflet** are M-mode hallmarks of MS.
 - b. Two-dimensional findings include restricted motion and diastolic doming of leaflets (hockey stick sign) (Fig. 16.6). The leaflets and chordae are thickened and are often calcified in older patients.
 - c. Doppler echocardiography is **essential** in the assessment of stenosis severity.
 - (1) A **transmitral peak velocity** > 1 m/s suggests MS. However, this is not specific because tachycardia, increased inotropy, MR, and VSD may cause increased flow in the absence of MS.

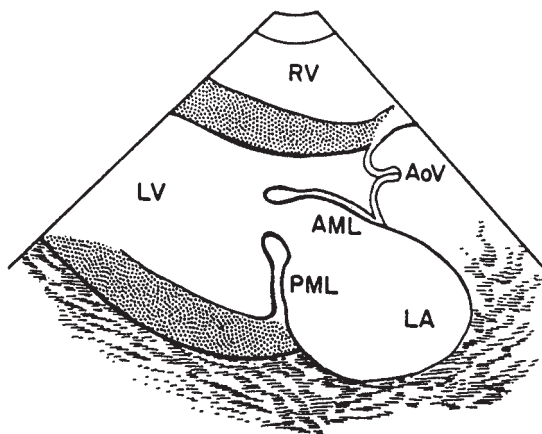


FIGURE 16.6 Two-dimensional echocardiographic scan in parallel long-axis view shows findings of mitral stenosis. Doming of leaflets is present. LV, left ventricle; RV, right ventricle; AML, anterior mitral leaflet; PML, posterior mitral leaflet; LA, left atrium; AoV, aortic valve. (Reproduced from Wilkins GT, Weyman AE, Abascal VM, et al. Percutaneous balloon dilatation of the mitral valve: an analysis of echocardiographic variables related to outcome and the mechanism of dilatation. *Br Heart J*. 1988;60:299–308, with permission from BMJ Publishing Group Ltd.)

- (2) The **transvalvular mean gradient** (assessed by means of tracing mitral inflow) provides an estimate of the severity of stenosis. A mean gradient < 5 mm Hg is typical in mild stenosis. Moderate stenosis is associated with a mean gradient between 5 and 12 mm Hg. A gradient > 12 mm Hg suggests severe MS.
- d. Echocardiography is used to estimate the **mitral valve area**.
 - (1) Direct planimetry of the orifice can be performed in the parasternal short-axis view.
 - (i) Optimal positioning is done by first obtaining a parasternal long-axis view and placing the mitral valve orifice in the center of the scan plane. The transducer is then rotated 90° to obtain the short-axis view. Measurements are obtained at the tips of the mitral leaflets.
 - (ii) Poor-quality 2D images and a thick, calcified subvalvular apparatus can make it difficult to obtain accurate measurements. Improper orientation of the scanning plane can produce oblique cuts across the valve and lead to overestimation of valve area. Scanning up and down until the typical fish-mouth appearance is seen helps in this regard. Dense fibrosis or calcification at the margins of the valve orifice can lead to underestimation of the valve area. Low-gain settings can cause dropout at the edges of the valve and overestimation of the valve area. High-gain settings can lead to underestimation. Planimetry is more difficult if commissurotomy has been performed, but remains the preferred method to assess the mitral valve area by means of echocardiography. With the advent of **3D imaging via transthoracic echocardiography**, more accurate orifice mapping for planimetry is now possible (see below).
 - (2) Pressure half-time method. Impedance to LA emptying prolongs the decline in transvalvular pressure gradient. This prolongs pressure half-time (time that it takes for pressure to fall to one-half the starting value, which equates with the time for the velocity to decrease to 70% of peak velocity). The mitral inflow E wave is used in the calculation.
 - (i) Empiric pressure half-time has been shown to correlate with valve area:

$$\text{Mitral valve area (in cm}^2\text{)} = 220/\text{pressure half-time}$$
 - (ii) If a software package to perform the calculations is not available, pressure half-time can be calculated by multiplying the deceleration time by 0.29. If atrial fibrillation is present, 5 to 10 consecutive beats are obtained and averaged.
 - (iii) It is important to have the Doppler beam parallel to the direction of blood flow.
 - (iv) The pressure half-time method **is inaccurate if there are rapid changes in LA hemodynamics**, such as immediately after balloon valvuloplasty.
 - (v) Obtaining a pressure half-time may be very difficult if sinus tachycardia is present (E–A fusion). Severe aortic insufficiency also fills the left ventricle in diastole, decreases pressure half-time, and leads to overestimation of the mitral valve area.
- e. Stress echocardiography is useful in the evaluation of patients with symptoms when the **resting study is discrepant with symptoms or clinical findings** (ACC/AHA class I). Gradients can be assessed during (supine bicycle) or immediately after (treadmill) exercise. Measurement of tricuspid regurgitation velocity is used to estimate pulmonary pressures with stress.
- f. **TEE** is indicated to exclude LA thrombus and assess MR prior to valvuloplasty, or if the TTE data are suboptimal (ACC/AHA class I), but is not indicated routinely if TTE data are adequate (ACC/AHA class III).

- g. **Three-dimensional echocardiography (3DE)** can provide a 3D data set to determine the mitral valve area. This method can avoid error in measurement related to correct alignment of the cut-plane with the level of the mitral valve tips and speeds up the time required for optimal planimetry. Using real-time 3D transesophageal technology, visualization of the mitral valve en face from the left atrium or left ventricle is possible at the time of percutaneous balloon mitral valvuloplasty. The main advantage of preoperative transesophageal 3DE is that it replicates the surgical view of the mitral valve that will be seen upon opening the left atrium.
2. **Cardiac catheterization.** Hemodynamic measurements obtained in a cardiac catheterization laboratory are used to **assess the severity of stenosis**. Simultaneous measurement of LV end-diastolic pressure, LA pressure (either directly or more commonly with PCWP as a surrogate), cardiac output (Fick method or thermodilution), heart rate, and diastolic filling period (seconds per beat) is required. LV pressure and PCWP (or LA pressure) tracings are made simultaneously (Fig. 16.7). A mean transmitral gradient is derived from the preceding measurements (planimeter area between the left ventricle and PCWPs during diastole; this area is multiplied by the scale factor of the tracing in millimeters of mercury per centimeter to obtain the gradient). The PCWP tracing ideally should be realigned by 50 to 70 milliseconds to the left (with tracing paper) to account for the time delay in transmission of LA pressure to the pulmonary venous beds.

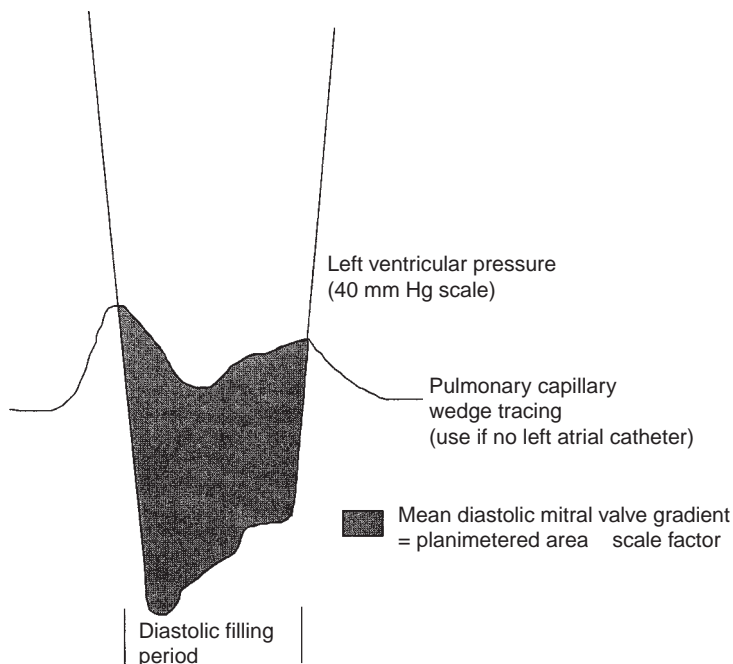


FIGURE 16.7 Simultaneous left ventricular and pulmonary capillary wedge pressure tracings used to measure mean gradient across mitral valve during diastole.

a. The **Gorlin formula**:

$$\text{Area} = \frac{\text{Cardiac output/diastolic filling period} \times \text{heart rate}}{37.7 \times \sqrt{(\text{mean transmitral pressure gradient})}}$$

Gorlin derived the empirical constant of 37.7, which is the Gorlin constant (44.3) multiplied by 0.85 (the correction factor for the mitral valve).

b. A **simplified version of the Gorlin formula** proposed by Hakki et al. has been validated and provides a reasonable approximation of the valve area:

$$\text{MVA} = \frac{\text{cardiac output}}{\sqrt{(\text{mean mitral gradient})}}$$

c. **Pitfalls.** PCWP cannot be used if the patient has pulmonary venous occlusive disease or cor triatriatum. The catheter must be properly wedged. In addition, **thermodilution cardiac output is less accurate** if there is severe tricuspid regurgitation or low cardiac output. **Immediately after valvuloplasty** MR or atrial septal defect, flow may lead to inaccurate estimations of mitral flow.

d. **Cardiac catheterization** is indicated in the evaluation of patients when echo-Doppler and clinical findings are discrepant (ACC/AHA class I) or when echo findings are internally discordant (class IIa) or if pulmonary hypertension is disproportionate to MS severity as assessed by echo (class IIa).

3. **ECG.** LA enlargement (P mitrale) is usually present when sinus rhythm persists. Signs of RV hypertrophy are seen with pulmonary hypertension. Atrial fibrillation is common and the fibrillatory waves are usually coarse.

4. **Chest radiography.** LA enlargement is apparent with a **double density** along the right heart border. A convexity can be apparent below the pulmonary artery, representing the LA appendage. Radiographic splaying of the carina with elevation of the left main bronchus and posterior displacement of the esophagus at barium swallow examination reflect LA enlargement. Kerley B lines may be present from increased pulmonary venous pressure. RV enlargement (decreased retrosternal air space on the lateral radiograph) may be present. Evidence of mitral valve calcification, or rarely LA calcification (McCallum's patch), may be present.

E. **Therapy.** The overall management approach to the individual with MS should integrate symptomatic status, degree of stenosis, and suitability of the valve for percutaneous balloon mitral valvuloplasty.

1. **Medical therapy**

a. Patients **without symptoms** who have mild MS (valve area > 1.5 cm² and mean gradient < 5 mm Hg) need no specific treatment and, **in accordance with current AHA guidelines, do not require endocarditis prophylaxis**. In patients with rheumatic valve disease, guidelines for the **prevention of rheumatic fever** should be applied. Annual reevaluation is recommended, but a yearly echocardiogram is not indicated unless there is a change in clinical status.

b. Patients with only **mild symptoms of exertional dyspnea** can be treated with **diuretics** and salt restriction to lower LA pressure. **β-Blockers** blunt the chronotropic response to exercise and may improve exercise capacity. **Arterial vasodilators should be avoided**.

c. **Atrial fibrillation** can clearly exacerbate symptoms, and **cardioversion or rate control measures** are important to maintain diastolic filling time. **Embolism** is a much feared complication of MS and occurs in up to 20% of patients; risk is increased with advancing age and atrial fibrillation.

- (1) Digitalis and **β -blockers** are the preferred agents to achieve rate control.
- (2) **Anticoagulation** with warfarin **is imperative** for patients with paroxysmal, persistent, or chronic **atrial fibrillation and MS** because they are at **high risk for thromboembolism** and this is also **indicated** in those with a history of **prior embolism or known LA thrombus** (ACC/AHA class I). Newer less emphatic recommendations (ACC/AHA class IIb) have been made for anticoagulation in MS patients with large atrial diameter (≥ 55 mm) or those with severe MS and enlarged LA size and evidence of spontaneous contrast on echocardiogram. The targeted INR is typically between 2.5 and 3.5.
- (3) Antiarrhythmic drug therapy may be used in an attempt to restore sinus rhythm, but long-term efficacy may depend on correction of the MS.
- (4) The role of percutaneous balloon mitral valvuloplasty in patients with new-onset atrial fibrillation and moderate to severe MS who are otherwise asymptomatic is controversial.

TABLE 16.6

ACC/AHA Indications for Percutaneous Mitral Balloon Valvotomy

Class I

1. PMV is effective for symptomatic patients (NYHA functional class II, III, or IV), with moderate or severe MS and valve morphology favorable for PMV in the absence of left atrial thrombus or moderate to severe MR
2. PMV is effective for asymptomatic patients with moderate or severe MS and valve morphology that is favorable for PMV, who have pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise) in the absence of left atrial thrombus or moderate to severe MR

Class IIa

PMV is reasonable for patients with moderate or severe MS who have a nonpliable calcified valve, are in NYHA functional class III–IV, and are either not candidates for surgery or at high risk for surgery

Class IIb

1. PMV may be considered for asymptomatic patients with moderate or severe MS and valve morphology favorable for PMV who have new-onset atrial fibrillation in the absence of left atrial thrombus or moderate to severe MR
2. PMV may be considered for symptomatic patients (NYHA functional class II, III, or IV) with MV area > 1.5 cm² if there is evidence of hemodynamically significant MS based on PA systolic pressure > 60 mm Hg, pulmonary artery wedge pressure of 25 mm Hg or more, or mean MV gradient > 15 mm Hg during exercise
3. PMV may be considered as an alternative to surgery for patients with moderate or severe MS who have a nonpliable calcified valve and are in NYHA class III–IV

Class III

1. PMV is not indicated for patients with mild MS
2. PMV should not be performed in patients with moderate to severe MR or left atrial thrombus

PMV, percutaneous mitral valvotomy; NYHA, New York Heart Association; MS, mitral stenosis; MR, mitral regurgitation; MV, mitral valve.

2. **Percutaneous or surgical therapy** (Table 16.6). **If more than mild symptoms** (New York Heart Association [NYHA] class II or greater) are present due to MS, the patient should be referred for surgical or percutaneous therapy. An asymptomatic patient, with moderate to severe MS and evidence of pulmonary hypertension at rest or with exercise, should also be referred for percutaneous therapy if the valve is suitable. Mortality increases substantially as symptoms progress. Results of natural history studies, conducted before valvotomy procedures were developed, indicate that young symptomatic patients have about 40% mortality at 10 years and almost 80% at 20 years. Elderly patients have 60% to 70% mortality at 10 years. Marked **pulmonary hypertension** (pulmonary arterial systolic pressure > 60 mm Hg) is an indication for mechanical treatment, even in the absence of symptoms in moderate to severe MS. Rarely, for **patients with asymptomatic MS** who do not have pulmonary hypertension, surgical or balloon intervention may be warranted. Instances where this is indicated include **women with severe MS contemplating to become pregnant**, those with severe MS who will need a major surgical procedure with massive fluid shifts, or those with repeated embolism despite anticoagulation. In the last instance, surgical intervention is usually indicated, and LA appendage ligation is performed simultaneously.

a. **Percutaneous balloon mitral valvuloplasty is considered the treatment of choice for symptomatic patients with moderate to severe MS who have favorable valve morphology.** The technique involves placement of a balloon-tipped catheter into the left atrium through a transseptal puncture and then across the mitral valve. The hourglass-shaped balloon (Inoue balloon) is inflated and deflated to increasingly larger diameters until the desired result is obtained.

- (1) Typically, there is an increment in valve area of 1 cm², mainly as a result of splitting of the fused commissures. The mean valve area usually doubles with a 50% to 60% reduction in transmitral gradient.
- (2) This procedure is **generally contraindicated in patients with > 3+ MR** (the procedure normally increases MR by one grade) **or in whom there is an LA or appendage thrombus** (risk of procedural embolism). Severe tricuspid regurgitation (does not improve substantially) and severe pulmonary hypertension (if pulmonary artery pressures do not fall, then substantial risk of right-to-left shunt across procedural atrial septal defect) are relative contraindications to the procedure.
- (3) An **echocardiographic score** has been developed to help select patients who may be candidates for percutaneous valvuloplasty. There are four parts to the assessment (mobility, leaflet thickening, subvalvular thickening, and calcification) (Table 16.7). In general, extensive subvalvular disease results in a poorer outcome with valvuloplasty. Patients with extensive fluoroscopically visible mitral valve calcification also have a worse outcome after percutaneous therapy.
 - (a) A total echocardiographic score (adding the four components) **higher than 11** is associated with a poorer outcome and a suboptimal increase in valve area, a higher incidence of heart failure and restenosis, and higher mortality. Patients with high scores **should not undergo valvuloplasty** unless surgical treatment is impossible.
 - (b) Echocardiographic scores of **9 to 11** represent a **gray zone** in which some patients have good results with valvuloplasty. Others have suboptimal results.
 - (c) Optimal results of balloon valvuloplasty are usually achieved when the echocardiographic score is **8 or less**.
- (4) TEE plays a critical role during valvuloplasty. The most immediate concern is to **rule out LA and appendage thrombi**. If thrombosis

TABLE 16.7 **Echo Score Assessment for Percutaneous Valvuloplasty in the Management of Mitral Stenosis**
Mobility (grade 0–4, 0 being normal)

1. Highly mobile with only leaflet tips restricted
2. Mild leaflet restriction; base portions have normal mobility
3. Valve moves forward in diastole, mainly from base
4. No or minimal diastolic movement of valve

Subvalvular thickening (grade 0–4, 0 being normal)

1. Minimal thickening below leaflets
2. Chordal thickening up to one-third of chordal length
3. Thickening extending to distal one-third of chords
4. Extensive thickening to papillary muscles

Thickening of leaflets (grade 0–4, 0 being normal)

1. Near normal (4–5 mm)
2. Marginal thickening (5–8 mm) with normal thickness of midleaflets
3. Thickening of entire leaflet (5–8 mm)
4. Extensive thickening of all leaflet tissues (> 8–10 mm)

Calcification (grade 0–4, 0 being normal)

1. Single area of echo brightness
2. Scattered areas of increased brightness along leaflet margins
3. Brightness extending to the midportion of leaflets
4. Extensive brightness throughout the leaflet tissue

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is present, anticoagulation for at least 1 month is undertaken with repeat TEE to confirm resolution before valvuloplasty. TEE can also help guide balloon positioning; after each inflation, the degree of MR and the gradient can be assessed. The degree of residual MS can be estimated with planimetry of the valve orifice before and after inflation. The pressure half-time method is unreliable until 24 to 48 hours after the procedure.

- (5) Echocardiography is useful in the determination of immediate **post-procedural complications** (Table 16.8). Among these is MR with an incidence estimated at 3% to 8%, depending on the series. The echocardiographic score is less predictive of the severity of postprocedural MR.

TABLE 16.8 **Complications of Balloon Valvuloplasty**

Mitral regurgitation

Cardiac perforation: incidence as high as 2–4%

Embolization: incidence 2% in the National Heart, Lung, and Blood Institute registry

Residual atrial septal defect: most close within 6 mo; can persist long term among as many as 10% of patients; generally small and well tolerated

- (6) The frequency of **restenosis of the valve** is variable, depending on the age of the patient and the immediate procedural increment in valve area. Data from the National Heart, Lung, and Blood Institute registry of all functional classes of patients show an 84% survival rate 4 years after treatment. Advanced age, high NYHA functional class, presence of atrial fibrillation, smaller initial mitral valve area, higher pulmonary arterial pressure, and substantial tricuspid regurgitation are **associated with poorer long-term results**. These variables identify a population with more serious illness that frequently necessitates intervention and should not preclude valvuloplasty. More postprocedural MR and lower postprocedural mitral valve area are associated with poorer long-term results.
- b. **Surgical treatment.** Closed **commissurotomy** was the earliest surgical approach used. This was performed through a thoracotomy (without cardiopulmonary bypass) and atriotomy with a valve dilator. This procedure is rarely used in the United States since the development of the percutaneous approach and improvements in open-heart surgery. **Open mitral valvotomy** involves direct visualization of the mitral valve (with cardiopulmonary bypass), debridement of calcium, and splitting of fused commissures and chordae.
 - (1) Severe subvalvular disease or valvular calcification often leads to the choice of **surgical intervention over valvuloplasty**. Coexistent disease in other valves (e.g., aortic stenosis or aortic regurgitation) that necessitates treatment also favors surgical intervention.
 - (2) Mitral valve replacement. Valve replacement is often required, especially when there is **extensive fibrosis and calcification or concomitant MR**.
 - (3) Mitral valve repair is more difficult but can be performed in selected cases with commissurotomy when there is mixed MS/MR.
 - (4) For patients with long-standing **atrial fibrillation**, a combined maze procedure (either surgical or using an intraoperative ablation catheter) can be performed in conjunction with the valve operation. LA appendage ligation may also be added to reduce future cardioembolic risk.
 - c. Comparison of balloon valvuloplasty and open commissurotomy. Studies in ideal patients for balloon valvuloplasty and commissurotomy suggest equal improvement in valve area and symptoms immediately postprocedure and in medium-term follow-up.
 - d. **Postprocedural follow-up care.** **Patients who have undergone balloon valvuloplasty or operations for MS should undergo baseline echocardiography**, preferably > 72 hours after the procedure. In patients with a history of atrial fibrillation, warfarin should be restarted 2 to 3 days after the procedure. **Clinical follow-up examination** should be performed at least once a year and more often if symptoms develop. It has become common practice at many centers for patients to undergo **follow-up echocardiography on a once-a-year basis**, although no firm guidelines have been developed for this.

ACKNOWLEDGMENTS: *The authors wish to thank Carmel Halley, MD, and Maran Thamilarasan, MD, for their contributions to earlier editions of this chapter.*

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CHAPTER

17

Shikhar Agarwal
Brian P. Griffin

Tricuspid Valve Disease, Pulmonary Valve Disease, and Drug-Induced Valve Disease

TRICUSPID VALVE DISEASE

I. INTRODUCTION. The **tricuspid valve (TV) apparatus** consists of three valve leaflets—septal, anterior, and posterior—along with the tricuspid annulus, the chordae tendineae, and the papillary muscles. Normally, the TV has an orifice area of 5 to 7 cm². The normal TV annulus is an elliptical and nonplanar structure, lying somewhat inferiorly and anterolaterally compared with the mitral valve (MV) annulus. The noncircularity and the nonplanarity of the TV have important mechanistic and therapeutic implications for correction of TV anomalies. Both tricuspid stenosis (TS) and tricuspid regurgitation (TR) can produce typical symptoms of right-sided congestive heart failure in their advanced stages. TV dysfunction can occur in both anatomically normal and abnormal valves.

II. TRICUSPID STENOSIS (TS). TS is rare as an isolated entity and is most commonly part of a multivalvular process. TS is usually organic in nature and is commonly encountered in conjunction with TR.

A. Etiology. Table 17.1 lists the causes of TS.

1. **Rheumatic heart disease (RHD)** by far is the most common cause of TS, accounting for > 90% of cases. Isolated TS is uncommon in these patients, and most patients have a combination of TS and TR. A large majority of patients with rheumatic TS have concurrent MV and aortic valve involvement. Clinically significant TV anomaly is present in only 5% of patients with RHD. Rheumatic TS is characterized by thickening and fibrosis of the valve leaflets, eventually culminating in marked leaflet contracture and commissural fusion.
2. **Carcinoid heart disease** is encountered in the setting of primary intestinal carcinoid tumors with secondary metastatic spread to the liver. Once metastatic to the liver, this neuroendocrine malignancy secretes numerous vasoactive substances (e.g., serotonin, histamine, and bradykinin), which directly affect the right-sided heart valves. Carcinoid valvular disease is characterized by thickened, retracted, shortened, and even fixed tricuspid leaflets, causing a mixed picture of regurgitation and stenosis. The pulmonic valve may also be involved. Unless there is a significant right-to-left shunt (via an atrial septal defect or patent foramen ovale), the left-sided heart valves are usually spared, owing to the clearance of vasoactive substances by the lungs.

B. Pathophysiology

1. TS produces a **diastolic pressure gradient** between the right atrium and the right ventricle, which is augmented when transvalvular flow increases. Therefore, the pressure gradient increases during inspiration or exercise and decreases during expiration. This typically occurs once the valve area falls below 1.5 cm².
2. A modest elevation of mean diastolic pressure gradient (i.e., ≥5 mm Hg) can raise right atrial pressure (RAP) (i.e., > 10 mm Hg) sufficiently to produce signs of **systemic venous congestion**, including hepatomegaly, ascites, and edema.
3. The right atrial *a wave* may be very prominent and may approach the level of the right ventricular systolic pressure (RVSP).
4. Resting cardiac output may be markedly reduced and may fail to augment with exercise, due to limited right ventricular preload.
5. Development of atrial fibrillation may result in higher RAPs due to the absence of organized atrial contraction and emptying.

C. Clinical presentation

1. **Signs and symptoms.** The presentation of TS varies depending on the **severity of stenosis**, the presence of **concomitant cardiac lesions**, and the **etiology of the valvular disease**.
 - a. **Fatigue** is common and related to low and relatively fixed cardiac output.

TABLE 17.1 Causes of Tricuspid Stenosis

Disease entity

Congenital
 Rheumatic
 Infective endocarditis
 Prosthetic valve failure
 Carcinoid syndrome
 Malignancy (e.g., myxoma and metastases)
 Whipple's disease
 Fabry's disease

- b. **Right upper quadrant pain** can result from high systemic venous pressure and concomitant hepatomegaly, ascites, and abdominal distention.
 - c. Occasionally, patients will experience a **fluttering discomfort** in the neck, caused by the giant *a waves* transmitted to the jugular veins.
 - d. Severe TS may mask the typical symptoms of other coexisting valvular lesions, such as mitral stenosis (MS). In the case of MS, the flow limitation across the TV can minimize the pulmonary congestion, orthopnea, and paroxysmal nocturnal dyspnea usually associated with MS.
2. **Physical findings.** The diagnosis of TS is often missed without a high index of suspicion. Clues that should raise suspicion of TS include the presence of **elevated jugular venous pressure** and **accentuation of a diastolic murmur along the left sternal border with inspiration** (not present in MS).
- a. Elevated central venous pressure may lead to marked hepatomegaly, ascites, and peripheral edema. In sinus rhythm, a giant *a wave* in the jugular venous pulse at the first heart sound (S_1) results from impaired right atrial diastolic filling during atrial systole.
 - b. **Diastolic murmur.** The murmur of TS is **low pitched, diastolic**, and best heard along the left lower sternal border in the third to fourth intercostal space or over the xiphoid process. If the rhythm is sinus, the murmur is prominent at end diastole (presystole). The low-pitched diastolic murmur may be obscured by the usually associated MS murmur. Accentuation of the murmur **intensity with inspiration** (Rivero-Carvalho sign) or other preload augmenting maneuvers (e.g., leg raising and squatting) may serve to differentiate the two murmurs or at least identify a component of TS in the setting of concurrent MS.
 - c. An **opening snap** (OS) may be heard at the left lower sternal border; however, this can be difficult to auscultate due to the commonly coexistent mitral OS.
 - d. Despite elevated neck veins and venous congestion, the patient may be comfortable lying flat due to the absence of pulmonary congestion. This apparent discrepancy between the severity of peripheral edema and the paucity of pulmonary congestion can help discriminate and identify TS from other valvular lesions.
 - e. Respiratory variation in splitting of the second heart sound (S_2) may be absent in patients with TS due to the relatively fixed diastolic filling of the right ventricle despite respiration.
 - f. In patients with the carcinoid syndrome, symptoms related to neurohormonal release, such as flushing and diarrhea, are typically more common than symptoms attributable to TS.
- D. **Diagnostic testing.** The hemodynamic expression of TS is a pressure gradient across the TV in diastole. A mean diastolic pressure gradient of 2 mm Hg across the TV establishes the diagnosis of TS during catheterization. Nowadays, hemodynamic diagnosis is rarely required, as the diagnosis is usually apparent on Doppler echocardiography.
- 1. **Electrocardiogram (ECG).** TS is suggested by the presence of right atrial enlargement on the ECG (P-wave amplitude > 2.5 mV in lead II). Because of the common coexistence of MS, biatrial enlargement may be seen.
 - 2. **Two-dimensional (2D) echocardiography.** The **echocardiogram is the most useful tool** in identifying TS. Typical findings **include reduction in the diameter of the TV orifice and thickening and diastolic doming of the tricuspid leaflets** (especially the anterior leaflet). Doppler interrogation of the TV will reveal increased transvalvular velocity; a mean pressure **gradient > 5 mm Hg using continuous-wave (CW) Doppler** is generally diagnostic of TS. Although it is possible to estimate the TV area by pressure half-time or planimetry, such measurements have limited utility in practice, as the severity of TS is more commonly described by the tricuspid diastolic pressure gradient. **Transesophageal echocardiogram (TEE)** is generally less useful than transthoracic echocardiogram (TTE) for assessing transvalvular gradients in TS, given that the TV is an anterior structure.

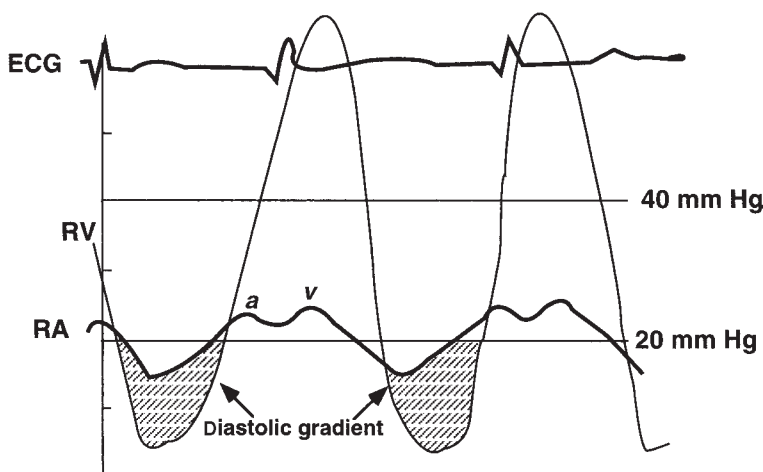


FIGURE 17.1 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid stenosis.

3. **Three-dimensional (3D) echocardiography.** Given the complex 3D structure of the TV, 3D echocardiography (transthoracic or transesophageal) may prove to be a useful adjunct to standard 2D echocardiography. Using this modality, all TV leaflets can be simultaneously imaged, potentially allowing for more accurate calculation of TV area and precise visualization of leaflet motion.
 4. Given the accuracy of modern echocardiographic techniques, cardiac catheterization can often be bypassed. **Right heart catheterization can be used to confirm the diagnosis** already suggested by Doppler echocardiography and can serve as a prelude to therapeutic balloon valvuloplasty. Cardiac output is typically low. The RAP is elevated and the *a* wave may be very tall, sometimes approaching the RVSP in magnitude. Simultaneous measurement of the right atrial and right ventricular pressures with dual catheters (or a dual-lumen catheter) enables the calculation of the diastolic pressure gradient (Fig. 17.1). The measured gradient is highly dependent on cardiac output and heart rate. Maneuvers such as lifting the legs or administration of atropine may accentuate the gradient.
- E. Therapy**
1. **Medical therapy** consists of intensive sodium restriction and diuretics.
 2. **Defining coexisting valvular lesions** is critical to properly managing TS. For instance, in patients with combined TS and MS, the former should not be corrected alone, as this may produce pulmonary congestion. If other valvular surgery is planned, concomitant treatment of TS should be considered if the gradient exceeds 5 mm Hg or the TV orifice area is $< 2.0 \text{ cm}^2$.
 3. **Severe stenosis requires balloon valvuloplasty or TV replacement.** The indications for surgery or balloon valvuloplasty are usually determined by the severity of concomitant mitral or aortic valve disease. Limiting symptoms due to predominant TS are considered an indication for valvuloplasty or surgery. Balloon valvuloplasty appears to be successful from both a symptomatic and a hemodynamic standpoint, but can result in significant TR, potentially necessitating valve replacement.

4. **Bioprostheses are favored** when valve replacement is necessary at the tricuspid position, as **mechanical prostheses are more prone to thrombosis** at this location. Combined severe stenosis and regurgitation, as occurs with carcinoid disease, usually necessitates a surgical approach.

III. TRICUSPID REGURGITATION

- A. **Etiology and pathophysiology.** Any disease process that causes derangement of the TV apparatus (annulus, leaflets, chordae, and papillary muscles) can lead to TR. The most common cause of TR is not intrinsic valvular disease but rather dilation of the right ventricle, causing secondary (functional) TR. Table 17.2 lists the causes of TR.
 1. The most commonly encountered type is the **functional or secondary TR**. Functional TR refers to the TR secondary to the left or the right heart pathology in the face of **normal TV leaflet morphology**. Functional TR is a dynamic entity that is regulated by several factors, including annular dilation, annular shape, pulmonary hypertension, ventricular dysfunction, and leaflet tethering.
 2. TR with an **anatomically abnormal valve (i.e., primary TR)** may be a manifestation of congenital heart disease (e.g., Ebstein's anomaly, atrioventricular canal defects, and ventricular septal defect [VSD]). In addition, a variety of conditions such as RHD, myxomatous degeneration, carcinoid heart disease, radiation, endomyocardial fibrosis, and the hypereosinophilic syndrome may cause scarring/thickening of the TV apparatus, resulting in poor leaflet coaptation and TR.
- B. **Clinical presentation**
 1. **Signs and symptoms.** The spectrum of symptoms of TR is wide and depends on its etiology and chronicity. **Isolated TR is usually well tolerated**. When TR and pulmonary hypertension coexist, cardiac output declines and patients

TABLE 17.2 Causes of Tricuspid Regurgitation

Primary causes

Rheumatic
 Ebstein's anomaly
 Carcinoid
 Connective tissue disease (e.g., Marfan's syndrome)
 Tricuspid valve prolapse
 Trauma
 —*Blunt/penetrating injuries*
 —*Iatrogenic secondary to pacemaker lead insertions*
 Tumors (myxoma, tumors of tricuspid valve leaflet)
 Infective or marantic endocarditis
 Papillary muscle dysfunction
 Radiation injury
 Toxic secondary to phen-phen or methysergide valvulopathy

Secondary (functional) causes

Right ventricular dilation (dilated annulus)
 Pulmonary hypertension
 Right ventricular dysfunction
 —*Global: cardiomyopathy, myocarditis, infarction*
 —*Segmental: ischemia, infarction, fibrosis, arrhythmogenic right ventricular dysplasia*

may manifest symptoms of right heart failure. Patients may present with painful **hepatic congestion and substantial peripheral edema**. **Fatigue** from reduced cardiac output is another common presentation. Patients may notice **pulsations in their neck** due to the prominent *cv wave* in the jugular venous pulse. TR often coexists with MV disease; in these patients, the symptoms associated with MV disease usually predominate.

2. Physical findings

- a. On general examination, patients with severe TR may have signs of weight loss, cachexia, and jaundice related to congestive hepatopathy and bowel edema.
- b. The neck veins will show loss of the usual *x wave* and a prominent systolic wave, usually referred to as a *cv wave*, followed by a rapid *y* descent. The characteristics of the large *cv wave* in the jugular venous pulse are dependent on TR severity. With significant TR, the prominent *cv wave* has maximal height at S₂, and the rapid *y* descent is most prominent on inspiration. A venous systolic thrill and murmur in the neck may be present in severe TR. The right ventricular impulse is often hyperdynamic.
- c. TR typically produces a **pansystolic murmur** at the third to fourth intercostal space along the left sternal border. The TR **murmur increases with inspiration (Carvallo sign)**.
- d. A TR murmur that develops **in the presence of pulmonary hypertension is usually high pitched** and pansystolic, whereas a TR **murmur of primary etiology** (from endocarditis or trauma) is **short** (limited to first half of systole) **and low pitched**.
- e. TR causes an increase in diastolic flow across the TV. This may be heard as an **early diastolic rumble** (short and low-pitched) along the left sternal border.
- f. With **severe, long-standing TR**, there is **ventricularization of the right atrium** (the pressure gradient across the TV is minimized), and the TR **may be barely audible or absent**.
- g. **Other findings.** A **right-sided third or fourth heart sound (S₃ or S₄) is often present along the left sternal border, which augments with inspiration**. If **pulmonary hypertension coexists**, P₂ is accentuated. **Systolic pulsation** of the liver is often an associated physical finding, although this may be diminished once congestive cirrhosis develops.

C. Diagnostic testing

1. **Electrocardiography.** The findings are usually nonspecific. Incomplete right bundle branch block may be seen. Atrial fibrillation is commonly found in association with severe TR.
2. **Echocardiography.** The most common views used for the detection of TR are the parasternal right ventricular inflow, basal short axis, and the apical four-chamber views.
 - a. **Physiologic TR.** A small degree of TR is observed in about 70% of patients with structurally normal hearts, and the prevalence increases with age. Physiologic TR is usually represented by a small jet that does not extend > 1 cm into the atrium.
 - b. **Two-dimensional echocardiography**
 - (1) Leaflet thickening may be seen in TR due to rheumatic or carcinoid disease. In functional TR, the leaflets usually appear normal. Tricuspid prolapse often occurs in patients with MV prolapse and may cause significant TR. In Ebstein's anomaly, the septal leaflet of the TV is displaced apically. Vegetations are evident with endocarditis, and a flail valve leaflet may be seen with iatrogenic damage (e.g., after endomyocardial biopsy) or following papillary muscle rupture with right ventricular infarction.
 - (2) With moderate to severe TR, a **right ventricular volume overload pattern** is seen, characterized by right ventricular enlargement, ventricular septal flattening or shift to the left in diastole, and paradoxical motion in

systole. There is often associated dilation of the right atrium and inferior vena cava (IVC).

- c. **Doppler analysis.** Assessment of TR involves incorporation of all of the Doppler information obtainable: size of the color jet, presence or absence of a proximal convergence zone (on the right atrial side of the valve), velocity profile, and eccentricity of the TR jet. Eccentric, wall-hugging jets should be typically upgraded by one grade, as is done for mitral regurgitation, because these are generally not visualized fully by echocardiography.

(1) TR direction and severity are assessed with color-flow Doppler. The severity of TR is estimated in several ways, including

- (a) Jet area—This measure is highly dependent on echocardiographic settings, particularly the pulse repetition frequency, and the direction and eccentricity of the jet.
- (b) Vena contracta width—The narrowest portion of the jet just downstream from the valve orifice gives a rough estimate of the effective orifice area. A jet width of > 0.7 cm suggests severe TR.
- (c) Proximal flow convergence (see Chapter 16).
- (d) CW Doppler—The signal intensity and contour of the TR jet on CW Doppler can help define TR severity. Severe TR produces a dense spectral recording along with a triangular, early peaking velocity.
- (e) Hepatic vein flow—Systolic flow reversal in the IVC or hepatic veins is consistent with severe TR.

(2) The RVSP is estimated using the modified Bernoulli equation after measuring the peak TR jet velocity by CW Doppler. In the absence of pulmonic stenosis, the pulmonary artery systolic pressure (PASP) can then be estimated as $PASP = RVSP + RAP$.

3. **Cardiac catheterization.** In the presence of moderate to severe TR, right heart catheterization will show a dominant *v* wave in the RAP curve (Fig. 17.2), an RAP curve resembling that of the right ventricle, increased right ventricular end-diastolic pressure, and low cardiac output by thermodilution and Fick techniques. **Angiocardiography** involves injecting contrast into the right

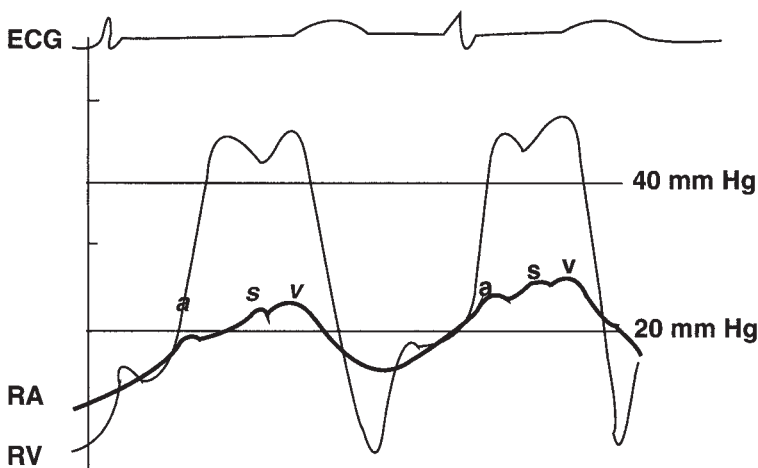


FIGURE 17.2 Tracings of simultaneous right atrial (RA) and right ventricular (RV) pressure waveforms in a patient with tricuspid regurgitation.

ventricle while viewing the right anterior oblique projection. This method allows for visualization and semiquantification of the TR jet but is rarely performed, as echocardiographic techniques are more reliable.

D. Therapy

1. In the absence of pulmonary hypertension, mild to moderate degrees of TR can be well tolerated for many years, and surgery is not recommended (American College of Cardiology/American Heart Association [ACC/AHA] class III). If right ventricular failure develops, **medical therapy** should be targeted at diuretic therapy and afterload reduction, as in other heart failure states.
2. **Surgical therapy.** When there is an **organic cause** of moderate to severe TR, **surgical repair or replacement** may be necessary depending on the symptoms and the degree of leaflet destruction/damage. Currently, there is a lack of a clear consensus regarding indications for surgical repair of mild to moderate functional TR. ACC/AHA recommends surgical repair of severe TR in the setting of multivalvular disease (class I). Several studies have demonstrated a significant improvement in the functional status among individuals undergoing concomitant TV repair with MV or AV surgery in comparison to those undergoing left heart valvular surgery alone. In addition to multivalvular disease, tricuspid annuloplasty is recommended in patients undergoing MV surgery when there is pulmonary hypertension or significant TV annular dilation (class I). Most commonly, surgery for TR is considered in combination with left heart valvular surgery. In patients with MS and TR, a decision to repair the TV should be based on the severity of the TR, as well as the duration and severity of pulmonary hypertension (i.e., TR in the setting of long-standing pulmonary hypertension and MS is unlikely to improve with MV surgery alone). Usually tricuspid repair or annuloplasty is favored over prosthetic implantation where this is feasible. The other situations where TV repair may be considered include severe TR with deteriorating exercise capacity (ACC/AHA class I), severe TR with atrial fibrillation (ACC/AHA class IIa), and progressive enlargement of an already dilated right ventricle (ACC/AHA class IIb).

PULMONARY VALVE DISEASE

I. INTRODUCTION. The pulmonary valve is a trileaflet valve that separates the right ventricle from the pulmonary vasculature. Dysfunction of the valve can have adverse effects on the right ventricle by producing pressure and/or volume overload. A small degree of pulmonic regurgitation (PR) may be a common finding in healthy adults. Acquired pulmonary valve disease is rare in comparison with other valvular disorders.

II. VALVULAR PULMONARY STENOSIS (PS)

A. Etiology

1. **Congenital** PS is the most common pulmonary valve problem, occurring in approximately 10% to 12% of all adult patients with congenital heart disease. Valvular PS is typically an isolated abnormality, but it may occur in conjunction with VSD.
2. **RHD** can affect the pulmonary valve, although this is uncommon and usually occurs in the setting of multivalvular involvement. This can result in thickening and fusion of the valve leaflets, resulting in PS.
3. As with the TV, **carcinoid heart disease** (see Section II.A.2) can affect the pulmonary valve, causing formation of typical “carcinoid plaques.” The plaques may result in constriction of the pulmonic valve ring, retraction and fusion of the cusps, and usually a combination of PS and PR.
4. Rarely, pseudopulmonary valve stenosis can occur as a result of **right ventricular outflow obstruction** from cardiac tumors or from an aneurysm of the sinus of Valsalva.
5. Although most cases of isolated PS are valvular, **obstruction may occur below the valve in the right ventricular outflow tract or above the valve at the junction with the main pulmonary artery.** Congenital PS is most frequently

caused by a dysplastic valve and less frequently a bicuspid valve. Right ventricular hypertrophy from the pressure overload of the PS on the right ventricle may cause concomitant right ventricular outflow tract obstruction, which usually reverses following successful dilation of the valvular stenosis.

B. Clinical presentation

1. **Signs and symptoms.** Patients with isolated PS present most commonly in the fourth or fifth decade of life with signs and symptoms of right heart failure and dyspnea on exertion. Of note, many patients with moderate PS remain asymptomatic. When the stenosis is severe, patients may occasionally have retrosternal chest pain or syncope with exertion. If the foramen ovale is patent, right-to-left shunting may occur, producing cyanosis and clubbing.
2. **Physical findings**
 - a. PS causes a systolic crescendo–decrescendo murmur, heard best in the third and fourth intercostal spaces, with delayed peaking of the murmur in severe cases. The murmur typically increases with inspiration. A thrill may be felt in the suprasternal notch and at the left upper sternal border. S_2 is often split widely, and the degree of the splitting increases with worsening stenosis due to delay in P_2 . The intensity of P_2 may be increased in mild stenosis but is usually diminished with severe stenosis. An ejection click can sometimes be heard along the left sternal border, and it may vary with respiration. As severity of PS increases, the click will move closer to S_1 .
 - b. The right ventricular impulse may be palpated at the left sternal border and be hyperdynamic.
 - c. The jugular venous pressure can be normal. However, in patients with reduced right ventricular compliance, a prominent *a* wave may be seen in the venous pulse. A right-sided fourth heart sound (RV S_4) may be heard at the left lower sternal border.
 - d. In advanced cases, evidence of right-sided heart failure may be present, including hepatic congestion and peripheral edema.

C. Diagnostic testing

1. **Electrocardiogram.** In patients with moderate to severe PS, the ECG may show right-axis deviation and right ventricular hypertrophy.
2. Chest radiography may reveal **poststenotic dilation** of the main pulmonary artery and diminished pulmonary vascular markings.
3. **Echocardiography** is useful in diagnosing pulmonary valve stenosis and for quantifying the severity of the obstruction. The best images of the pulmonary valve are obtained from the short-axis view at the level of the base from the parasternal and subcostal windows. Transesophageal echocardiography is useful when the TTE images are suboptimal.
 - a. **Leaflets.** In adults, the leaflets can appear thickened and calcified with restricted motion. In children with congenital PS, the leaflets are noncalcified with doming of the valve.
 - b. **Right ventricle.** The right ventricle may be normal, especially in children. Right ventricular dilation and hypertrophy may be seen in adults, depending on the severity and the duration of this disease.
4. **Doppler echocardiography** is the preferred method for grading the severity of PS. This method of quantifying the degree of stenosis is well correlated with the direct measurement obtained during cardiac catheterization. The peak gradient is measured across the pulmonary valve by using CW Doppler with the modified Bernoulli equation. The following levels of severity have been defined in the 2006 ACC/AHA guidelines on the management of valvular heart disease:
 - (a) Severe stenosis: a peak jet velocity of > 4 m/s (peak gradient > 60 mm Hg).
 - (b) Moderate stenosis: peak jet velocity of 3 to 4 m/s (peak gradient 36 to 60 mm Hg).
 - (c) Mild stenosis: peak jet velocity of < 3 m/s (peak gradient < 36 mm Hg).

D. Therapy

1. Mild to moderate PS generally has a good prognosis, and intervention is rarely necessary. Survival is excellent among patients with mild PS, with 94% patients alive as long as 20 years after diagnosis.
2. Patients with severe PS usually warrant a therapeutic intervention for relief of stenosis. The treatment of choice is **balloon valvuloplasty**, usually leading to a 75% decrement in the transvalvular gradient after a successful procedure. The procedure is usually successful if the valve is mobile and pliable. Prognosis and morbidity subsequent to the procedure are largely based on right ventricular function at the time of the procedure. The hypertrophic subpulmonary stenosis that may accompany valvular stenosis usually regresses after successful valvuloplasty. Valve replacement may be necessary if the valve is severely calcified or if there is severe concomitant TR.
3. The **ACC/AHA guidelines for intervention** in congenital PS are as follows:

Class I: Balloon valvuloplasty is indicated in symptomatic patients with > 30 mm Hg gradient (peak–peak) across the pulmonary valve at cardiac catheterization and in asymptomatic patients when this gradient is > 40 mm Hg.

Class II: Balloon valvuloplasty may be reasonable if the gradient across the pulmonary valve is 30 to 39 mm Hg by cardiac catheterization in an asymptomatic adolescent or young adult.

Class III: Balloon valvuloplasty is not indicated in asymptomatic patients whose pulmonary valve gradient is < 30 mm Hg at catheterization.
4. PS secondary to **carcinoid syndrome** has a very poor prognosis (with a median survival of 1.6 years), and the valve often does not respond to balloon valvuloplasty. **Valve replacement** is often necessary.

III. VALVULAR PULMONARY REGURGITATION (PR)

- A. **Etiology.** PR is most commonly produced secondary to dilation of the valve ring due to pulmonary hypertension or dilation of the pulmonary artery.
 1. **PR may occur secondary to rare congenital causes**, such as an absent, malformed, or fenestrated leaflet. In the setting of repaired tetralogy of Fallot, PR is a common and difficult problem, often contributing to progressive right ventricular dilation and dysfunction.
 2. Acquired causes of pathologic PR are much more common. **The most common acquired cause is pulmonary artery hypertension**, followed by infective endocarditis. Both carcinoid syndrome and RHD may cause PR but they are more likely to cause PS. Marfan's syndrome may cause PR secondary to dilation of the pulmonary artery. Iatrogenic PR may be caused by placement of a pulmonary artery catheter.
- B. **Clinical presentation**
 1. **Signs and symptoms.** Like TR, PR causes volume overload of the right ventricle. However, in the absence of significant pulmonary hypertension, it may be tolerated well for many years. Once symptomatic, the patients with PR present with the signs and symptoms of **right heart failure and exertional dyspnea**. In the setting of PR caused by infective endocarditis, patients may present with fever and hypoxia due to septic pulmonary emboli.
 2. **Physical findings**
 - a. The murmur of PR is a relatively brief **low-pitched, diamond-shaped, diastolic murmur**, heard best in the third and fourth left intercostal spaces with a widening of S₂. The murmur increases with inspiration, and **P₂ is accentuated** in the presence of pulmonary artery hypertension.
 - b. The **Graham Steell murmur** is a high-pitched, blowing decrescendo diastolic murmur starting immediately after P₂, which is accentuated by inspiration.

This characteristic murmur occurs when PASP exceeds 70 mm Hg in the presence of PR.

- c. A right ventricular S_3 and S_4 may be audible in the fourth intercostal space and will be augmented by inspiration. Depending on the severity and duration of the regurgitant valve, signs and symptoms of right heart failure may also be present on examination.

C. Diagnostic testing

The pulmonary valve is best evaluated with **echocardiography**, using the left ventricle short-axis view from the parasternal and subcostal windows. Minor degrees of PR are seen in 40% to 78% of normal individuals. Pathologic PR is relatively infrequent and should be diagnosed in the context of other structural abnormalities.

1. **Anatomic assessment.** The right ventricular outflow tract and pulmonary valve should be interrogated for abnormalities such as leaflet hypoplasia, increased cusp number, and abnormal valve motion (i.e., doming).
2. **Right ventricle.** The size and function of the right ventricle can provide an indicator of the severity of PR (i.e., long-standing severe PR should be associated with right ventricular dilation and/or hypertrophy).
3. Color-flow Doppler will reveal a regurgitant jet toward the right ventricle during diastole. Jet length is determined primarily by the pressure difference between the pulmonary artery and right ventricle and, therefore, is an unreliable indicator of PR severity. The **vena contracta** is probably a better measure of PR severity.
4. CW Doppler will show a dense spectral signal and rapid equilibration of diastolic pressures in severe PR. Maintenance of the regurgitant velocity during diastole suggests that **pulmonary hypertension** is the cause of valve incompetence. Furthermore, increasing pulmonary artery pressures correlate with decreasing acceleration times of pulmonary artery flow. Pulmonary artery pressures can be obtained using Doppler flow measurements and the following equation. Pulmonary artery diastolic pressure (PADP) is only obtainable in the setting of PR:

$$\text{PADP} = 4(V_{\text{PR-E}})^2 + \text{RA}_{\text{pressure}}$$

where $V_{\text{PR-E}}$ is the end-diastolic PR velocity.

D. Therapy

1. **Primary pulmonary valve regurgitation.** The prognosis is very good; rarely is correction of the defect necessary, except in cases of intractable right heart failure.
2. **Secondary pulmonary valve regurgitation.** The prognosis due to endocarditis, carcinoid, or pulmonary artery hypertension is dependent upon the prognosis and treatment of the primary disease. Treatment of the primary condition (e.g., repairing MV in the setting of pulmonary hypertension) often ameliorates the PR. Besides this, vasodilating therapies for pulmonary hypertension can reduce secondary PR. When a treatment is absolutely necessary, **the preferred approach is valve replacement with a bioprosthesis or a pulmonary allograft**. Percutaneous deployment of a prosthetic valve has been successfully accomplished in this setting and is under active investigation currently. Annulus repair is ideal in patients with coexisting left-sided valvular lesions.

DRUG-INDUCED VALVE DISEASE

- I. **INTRODUCTION.** Most common forms of valve disease are inherited or acquired in response to a specific disease process. Over the last three decades, however, it has become clear that several pharmacologic agents may produce a cardiac valvulopathy, which mimics other etiologies of valvular disease.

II. DRUGS KNOWN TO CAUSE VALVE DISEASE

- A. **Ergot** alkaloid derivatives (ergotamine and methysergide) used for migraine prophylaxis have been reported to cause valvulopathy since the early 1990s.

- B. In 1997, Connolly et al. reported that both **fenfluramine** and **dexfenfluramine**, the constituents of popular diet pills, were associated with valvular heart disease with a typical histologic appearance (described in subsequent text). This led to the withdrawal of a number of common diet drugs from the market. At their peak usage, about 14 million prescriptions had been written for these medications.
- C. More recently, valvular heart disease was reported in 24% to 28% of patients undergoing treatment of Parkinson's disease with **ergot-derived dopamine agonists (pergolide and cabergoline)**.
- D. There is an increased risk of valvulopathy in individuals with heavy and frequent use of the recreational drug, **3,4-methylenedioxymethamphetamine (MDMA)**. This drug, popularly known as *ecstasy*, has become one of the most frequently used party drugs in Western Europe and the United States over the last two decades.
- E. Thus far, there has been no convincing evidence of valvular heart disease with the use of other serotonergic drugs (e.g., selective serotonin reuptake inhibitors).

III. PATHOLOGY AND PATHOGENESIS

- A. Valves that are surgically removed from patients using these drugs are described as having a white, glistening appearance, with histologic evidence of a plaquelike process extending along the leaflet and encasing the chordae tendineae. These findings are **very similar to the findings seen in patients with valvular disease due to carcinoid tumors**, which also secrete vasoactive amines.
- B. Subsequent research has indicated that valvulopathic drugs may act via their ability to stimulate the serotonergic receptors, particularly the 5-hydroxytryptamine (5-HT)_{2B} serotonin receptor. This receptor is plentiful in normal heart valves and appears to be essential for normal cardiac development. Stimulation of the 5-HT_{2B} receptor appears to cause mitogenic stimulation of normally quiescent valve cells, causing an "overgrowth" valvulopathy.

IV. PREVALENCE. Estimates of the prevalence of drug-induced valvular disease have varied widely. Initial studies based on case series suggested a prevalence of valve disease as high as 20% to 30% in the setting of fenfluramine exposure, but larger population-based studies suggest a much lower prevalence of around 10% to 12% (vs. 5% to 6% in control group). **Factors that appear to be associated with a greater prevalence of valvular disease include duration of treatment, use of combination agents, and shorter time from cessation of drug treatment to evaluation.** The prevalence of disease is highest in those who have been on a valvulopathic medication for **> 6 months**.

V. CLINICAL PRESENTATION. Most commonly, patients seek advice based on a history of taking ergot-derived medications or diet drugs, given the media attention associated with this condition and the legal action that has been mounted against the drug manufacturers. Patients may also present with symptoms of valve disease, such as dyspnea and fatigue. **The predominant findings on examination in patients with significant valve disease involve regurgitation of the AV, the MV, or the TV.** Although the right-sided valves are usually involved, the ergot derivatives may also affect the left-sided valves and cause valvular regurgitation. Aortic regurgitation is reported with increased frequency in those with anorexic abuse than regurgitation at other valve locations.

VI. EVALUATION. Patients suspected of having valve lesions on examination or those in whom a cardiac examination is somewhat limited by obesity and who have been exposed to diet drugs should undergo echocardiography. The echocardiographic features simulate both rheumatic disease and carcinoid disease with **leaflet thickening and doming of the MV and thickening of the AV or the TV leaflets**. Despite the apparent restriction of motion of the leaflets, clinically significant **stenosis is rare**. Regurgitation, when present, may be of any grade or severity, although it is generally

mild. However, severe regurgitation requiring surgery has been reported with diet drug-induced valve disease.

VII. TREATMENT. Once drug-induced valve disease is suspected, the offending drug should be discontinued immediately. In the case of anorexiant-induced valve lesions, **mild improvement in the severity of the valvular regurgitation has been reported on medium-term follow-up after drug discontinuation.** Progression in the severity of valvular disease following drug discontinuation is relatively uncommon. Indications for the surgical intervention in drug-induced valvulopathy are similar to those of other disease processes. However, watchful waiting is a prudent approach in these patients, given the potential for some reversibility of the valve lesions upon drug discontinuation. Endocarditis prophylaxis is not indicated in those with evidence of drug-induced valve disease, per the most recent ACC/AHA guidelines.

VIII. FOLLOW-UP. Patients with valve disease should be evaluated both clinically and with echocardiography initially every 6 months. In those with mild stable lesions, yearly evaluation is appropriate.

ACKNOWLEDGMENTS: *The authors thank Drs. Amy P. Scally, Deepu Nair, and Marc Penn for their contributions to earlier editions of this chapter.*

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Prosthetic Heart Valves

Prosthetic valve replacement still represents the treatment of choice for severe native valve dysfunction, especially for rheumatic disease, which remains the most frequent cause of replacement worldwide. This chapter discusses the types of prosthetic valves, indications, and prosthetic valve choices and provides a brief overview of the recent developments in transcatheter aortic valve replacement (TAVR).

I. INDICATIONS FOR IMPLANTATION

A. Types of prosthetic valves. Prosthetic valves are classified into two major categories: mechanical and bioprosthetic. Each model differs in its durability, thrombogenicity, and hemodynamic performance. Various mechanical and bioprosthetic valves are shown in Figure 18.1.

1. Bioprosthetic valves. These resemble native valves but have a slightly less optimal hemodynamic performance, owing to the reduction in flow profile by interposed stents and the sewing ring.

a. Heterografts

- (1) Carpentier-Edwards valves are made of either bovine pericardium (aortic position), which have greater durability, or porcine leaflets mounted on a cloth-covered annular ring and supported by steel alloy flexible stents at each of the commissures.
- (2) The Hancock II stented porcine valve (Medtronic) has been considered as the porcine bioprosthetic valve with the best hemodynamics and longevity available. The supraannular prosthetic sewing ring improves hemodynamic performance; and modern preservation techniques using low-pressure fixation and treatment with sodium dodecyl sulfate increase longevity by delaying calcification. The durability of bioprosthetic bovine pericardial versus porcine valves is controversial, although many consider that the pericardial valves may have some durability advantage in younger patients.
- (3) For the **stentless porcine bioprostheses** (Medtronic Freestyle or St. Jude Medical), there are three different methods for implantation, with the subcoronary valve replacement being the most common. Although the stentless valves offer a better hemodynamic profile owing to the larger effective orifice area (EOA), convincing advantages in terms of mortality, left ventricular (LV) mass regression, and durability (when compared with pericardial and not porcine valves) have yet to be demonstrated.
- (4) Since the first-in-man **TAVR** done by Cribier in 2002, more than 40,000 patients have undergone TAVR worldwide (see Chapter 66). The technology has evolved tremendously and is now transforming the management of patients with critical aortic stenosis who are high-risk surgical candidates. The ground-breaking Placement of AoRtic TraNscathetER Valves (PARTNER) trial changed the paradigm. It randomly assigned

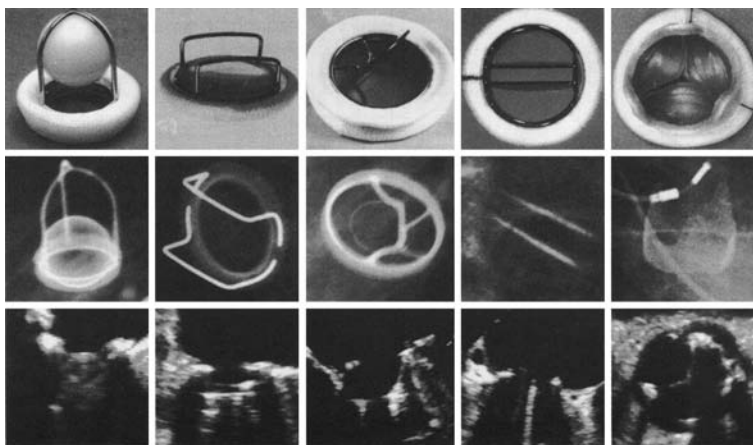


FIGURE 18.1 Photographic and radiographic appearance of different prosthetic heart valves. From left to right: Starr-Edwards caged ball, Kay-Suzuki caged disk, Björk-Shiley single-tilting disk, St. Jude's bileaflet tilting disk mechanical valves, and Carpentier-Edwards xenograft. (From Garcia M. Principles of imaging. In: Topol EJ, ed. *Comprehensive Cardiovascular Medicine*. Philadelphia, PA: Lippincott-Raven Publishers; 1998:610.)

patients ($n = 358$) with severe aortic stenosis, whom surgeons considered not to be suitable candidates for surgery, to standard therapy (including balloon aortic valvuloplasty) or transfemoral transcatheter implantation of a balloon-expandable bovine pericardial valve. The primary end point was the rate of death from any cause.

The results showed that this approach was associated with a significant reduced 1-year mortality for patients with severe aortic stenosis who are not surgical candidates due to advanced comorbidities (50.7% for medical treatment vs. 30.7% in the TAVR group; hazard ratio with TAVR, 0.55; 95% confidence interval [CI], 0.40 to 0.74; $p < 0.001$). The valve tested was Edwards SAPIEN heart valve system (Edwards Lifesciences) that consisted of a trileaflet bovine pericardial valve and a balloon-expandable, stainless steel support frame (Fig. 18.2).

The second largest experience, mostly European, is with the self-expanding Medtronic CoreValve ReValving system. It uses a porcine pericardial valve in a larger and self-expandable nitinol frame, which covers both the left ventricular outflow tract (LVOT) and the aortic root. It has also demonstrated similar trends in outcome, although with slightly higher incidence (up to 25%) of atrioventricular block requiring pacemaker implantation.

The long-term durability of these valves has been addressed only in small studies. Theoretically, and according to the manufacturer's wear test, both transcatheter valve systems are designed to last ≥ 10 years. All published studies suggest good durability and preserved hemodynamic function, with EOAs over 1.5 cm^2 at 3 years. Paravalvular leak has been a concern with these valves, but this is generally mild and does not usually progress significantly at least over medium-term follow-up.

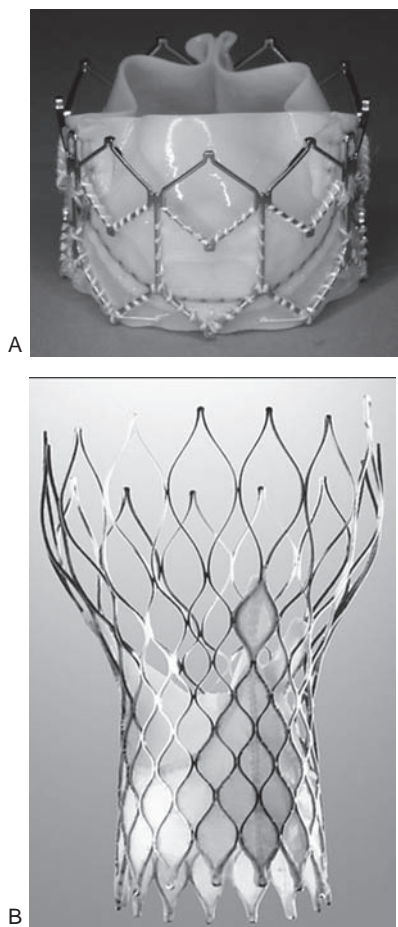


FIGURE 18.2 Transcatheter aortic valve prosthesis currently available for clinical use (*). **A:** Balloon-expandable Edwards SAPIEN XT valve (Edwards Lifescience, Irvine, CA). **B:** Self-expanding CoreValve ReValving System (Medtronic, Minneapolis, MN). (*) The CoreValve system is currently not approved yet by FDA for clinical use in the USA.

- b. Aortic homografts** are cryopreserved cadaveric human aortic valves. These are typically implanted stentless, with a short segment of the donor's aortic root for support. The coronary arteries require reimplantation. The hemodynamic profile of the homograft is similar to that of the native valve. Availability of homografts is a limiting factor.
- c. Autograft.** An autograft is a procedure in which the patient's own valve is moved from its normal anatomical position to another site. Typically, this is done with the pulmonary valve in patients with significant aortic valve disease. A pulmonary homograft is placed at the native pulmonary position. This operation is called the Ross procedure, after the surgeon who popularized it. This procedure has the advantage of putting a native valve at the hemodynamically most important position. It has been advocated for younger patients, and some reports suggest that the autograft may grow with the patient, which is advantageous in the adolescent age group. However,

the initial enthusiasm with this procedure has been tempered by suboptimal outcomes in many adult patients, particularly with regard to the pulmonary homograft. Additionally, progressive root enlargement may ensue in patients with bicuspid valve and ascending aortic dilatation, leading to autograft failure. The decision to proceed to autograft implantation in adults should be considered very carefully and in consultation with a surgeon with extensive experience of this procedure.

2. Mechanical valves

- a. **Single-leaflet tilting disk.** This valve (e.g., Björk-Shiley, Medtronic-Hall, and Omniscience) consists of a metallic sewing ring attached to a tilting disk made of pyrolytic carbon that rotates about an off-centered pivot axis, with a range of about 60° to 85° from the occluded to the open position. When open, the prosthesis has two orifices separated by the occluder. The major orifice is formed as the disk swings downstream to the open position. The disk on the other side of the pivot axis swings proximally, forming the minor orifice.
- b. **Bileaflet tilting disk.** The St. Jude and CarboMedics valves have two semi-circular pyrolytic carbon disks that rotate freely through 75° to 90°. Two large lateral orifices and a small central rectangular space are created in the open position. A built-in leakage volume is designed to reduce thrombus formation on disks.
- c. **Caged ball.** The Starr-Edwards valve consists of a silicone ball within a cage attached to a metallic alloy ring. The ball is free to travel along the cage over a distance of 1 to 2 cm. Flow across the prosthesis is directed circumferentially around the ball. The hemodynamic profile is less favorable than that of the tilting disk prosthesis. This is the valve with the greatest durability, with a 30-year follow-up in some studies.

B. Selection of valves. Table 18.1 summarizes the clinical factors that favor selection of a bioprosthetic versus a mechanical valve. The choice is largely dependent upon the age of the patient at the time of prosthetic valve implantation and on which complication the patient wants to avoid: specifically, anticoagulation therapy and its complications with the mechanical valve and structural valve deterioration with a bioprosthesis.

The recommendation to use tissue valves in older patients and mechanical valves in younger patients is based on information obtained from older trials. There have

TABLE 18.1 Clinical Factors Leading to Selection of a Bioprosthetic versus a Mechanical Valve

Factors favoring bioprosthesis	Factors favoring aortic homograft	Factors favoring mechanical prosthesis
Age > 70 y	Endocarditis	Age < 50 y
Bleeding diathesis	Small aortic annulus in older patients	Combined multivalvular placement
High risk of trauma		Other indications for chronic anticoagulation
Poor compliance		Completed childbearing in younger woman
Young woman considering pregnancy		

TABLE 18.2 Characteristics Favoring Valve Repair versus Replacement

Favoring valve replacement	Favoring valve repair
Rheumatic valve disease	Mitral valve prolapse
Endocarditis	Excessive leaflet mobility
Inexperienced surgeon	Ischemic mitral valve regurgitation
Complex mitral valve morphology	Bicuspid aortic valve with prolapse
Calcified and fibrosed valve	Annular dilatation with normal leaflets
Extensive leaflet destruction	

been no randomized controlled trials after 1982 comparing mechanical with bioprosthetic valves, which makes the decision difficult, as newer bioprosthetic valves may be more durable than older ones. There has been a shift toward using bioprosthetic valves in younger patients over the last decade.

1. **Valve repair.** The feasibility of native valve repair instead of replacement should always be considered prior to surgery (Table 18.2). Currently, the greatest experience is with mitral valve repair. If feasible, mitral valve repair offers several potential advantages over replacement, including **preservation of LV function via conservation of the subvalvular apparatus, lower operative mortality, higher long-term survival rate, and freedom from anticoagulation**. Mitral valve repair may be considered for asymptomatic patients with severe mitral regurgitation if there is a high chance of repair at high-volume centers.

An aortic valve with predominant regurgitation due to prolapse, but without severe stenosis or calcification, can also be repaired. Intraoperative transesophageal echocardiography (TEE) appears to have a role determining the quality of the repair and predicting the long-term durability.

2. **Bioprosthetic valves** are indicated in patients with **a contraindication to chronic anticoagulation** and are preferred for **patients ≥ 65 years (70 years in the mitral position)** due to reasonable durability, favorable hemodynamic profile, and freedom from chronic anticoagulation. Approximately 30% of heterograft bioprostheses fail within 10 to 15 years of implantation, although the incidence of bioprosthesis failure is age dependent (Table 18.3). Overall complication rates for aortic bioprosthetic and mechanical valves are similar at 12 years, with a higher rate of reoperation for bioprosthetic valves and a higher rate of hemorrhage with mechanical valves. The advent of newer low-profile bioprostheses and the apparent improved durability of later models have led to an increase in their use, especially in patients who wish to avoid anticoagulation.
3. **Transcatheter aortic valve replacement**, as mentioned before, is now indicated in patients with severe aortic stenosis who are considered inoperable or high risk for conventional open heart surgery due to advanced comorbidities. A comprehensive evaluation for procedural eligibility and candidacy is required including coronary angiography to exclude significant coronary artery disease. If significant coronary lesions are present, they should be revascularized percutaneously and the TAVR procedure is usually deferred for ≥ 1 month. Computed tomography (CT) angiography with three-dimensional vessel reconstruction is also required to determine the suitability of the iliofemoral access. Dedicated imaging, in particular of the infrarenal aortic segment to the femoral arteries, is needed for sizing of the arterial access (preferably > 6 mm in diameter), vessel tortuosity, and calcification of the iliac arteries. Lastly, TEE, both preprocedural and intra-procedural,

TABLE 18.3 Heterograft Valve Failure Rate 10 Years after Valve Replacement Relative to the Patient's Age

Patient's age (years)	Failure rate at 10 years (%)
< 40	40
40–49	30
50–59	20
60–69	15
≥70	10

Modified from Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med*. 1996;335:412, by permission of the Massachusetts Medical Society.

is important in the evaluation of the aortic annulus size, aortic valve morphology, and calcification of the aortic root and aortic valve leaflets. It can enhance procedural success in determining appropriate valve and device sizing selection in addition to continuous monitoring for procedural complications.

The transapical approach requires a small left thoracotomy to allow direct puncture and sheath introduction into the left ventricle for antegrade delivery of the TAVR system. Patients who require this approach have a higher incidence of peripheral vascular disease, which is a marker of worse long-term outcome. Nonetheless, in patients who require AVR but have aortic atheroma or peripheral vascular disease that limits their candidacy for retrograde transcatheter AVR, the transapical approach should be considered.

4. **Homografts.** The homograft is the **valve of choice in aortic valve endocarditis** and has the lowest valvular gradient among the bioprosthetic valves. Durability was thought to be superior to that of heterografts, but recent studies throw some doubt on this. Only 10% are still functioning after 20 years. The primary operation is more difficult with homografts, as the coronary arteries require implantation. Reoperation is also more complex, as the homograft frequently calcifies and is difficult to remove and replace. The main current indication for an aortic homograft is complex endocarditis involving a native valve, especially in prosthetic valve endocarditis and abscess where the risk of reinfection of a new prosthesis is high. Another indication is in older patients with small aortic root and LVOT in order to maximize hemodynamics and minimize the transaortic gradient.
5. **Mechanical valves.** Mechanical valves are **more durable than bioprosthetic valves**; some can last > 20 years. Mechanical prostheses are generally recommended for **patients < 50 years** because of greater durability and for **patients already on permanent anticoagulation** for previous stroke or arrhythmia. The stroke risk of about 1% per annum for patients with a mechanical valve receiving appropriate anticoagulation management is similar to that for a bioprosthetic valve without anticoagulation. In **younger patients requiring combined aortic and mitral valve replacement**, mechanical valves are preferred, given the more rapid rate of prosthesis deterioration in the mitral position. **Pregnancy should be discouraged in patients with mechanical prostheses** because of the high risk to the mother and the fetus (see Chapter 38). Given their lower profile, mechanical prostheses may be preferred in **patients with small ventricles**. Issues of **compliance with anticoagulation and risks of trauma** should be integrated into the selection of a mechanical valve.

- a. St. Jude Medical and Medtronic-Hall valves are the most popular prosthetic valves because of their favorable hemodynamic performance, longevity, and low rates of complications. Loss of structural integrity has been reported in a small percentage of patients with St. Jude valves, whereas the primary concern with the Medtronic-Hall valve is the potential for occluder impingement during placement.
 - b. Starr-Edwards valves are the most durable of all the prosthetic valves. However, they are less popular today because of their thrombogenicity and sub-optimal hemodynamic performance in comparison with tilting disk valves.
 - c. Manufacture of the Björk-Shiley valve was discontinued in 1986 following published reports of complications with **strut fracture**.
6. The decision with regard to the optimal valve type should be made in consultation with the cardiothoracic surgeon and patient and should not solely be based on age. Lifestyle, compliance, other medical issues, and consideration of pregnancy all have an impact on the decision.
- C. **Follow-up after valve surgery.** There is a **wide spectrum of clinical practices** in the follow-up of the asymptomatic patient after valve surgery. A **Doppler** study should be performed between 1 and 6 weeks following surgery as a baseline for future reference. For **mechanical valves, anticoagulation** should be monitored regularly for life. **Endocarditis prophylaxis** is imperative for prosthetic valves, and patients should receive appropriate education. Annual or biannual echocardiography seems prudent **after the fifth postoperative year** for valve repair and replacement.
- D. **Anticoagulation.** Table 18.4 summarizes the recommended targets for anticoagulation therapy in patients with prosthetic heart valves. The **embolic event rate is greater for mitral than for aortic** prostheses.
1. **Immediate postoperative period**
 - a. **Mechanical valves.** The approach to **postoperative anticoagulation** for mechanical prostheses varies widely. Early anticoagulation increases the risk of bleeding and tamponade. One approach is **warfarin, but not heparin, 3 to 4 days following surgery** when the epicardial wires are removed. Other centers recommend **low-dose intravenous heparin**, targeted for upper normal limits of activated partial thromboplastin time within 6 to 12 hours after valve replacement, and **full-dose intravenous heparin once the chest tubes are removed**. **Warfarin** is initiated within 24 to 48 hours following valve replacement. **Chronic anticoagulation for mechanical valves is associated with rates** of minor hemorrhage of 2% to 4% per year, major hemorrhage of

TABLE 18.4 Recommended Anticoagulation Therapy for Patients with Mechanical Prosthetic Valves

Level of risk	Prosthesis type	Recommended INR
Low	Single-tilting disk	3.0–4.0
	Double-tilting disk	2.5–3.0
High ^a	Caged disk	3.0–4.5
	Caged ball	3.0–4.5
	Multiple prostheses	3.0–4.5

INR, international normalized ratio.

^aPatients with atrial fibrillation, left atrial thrombus, severe left ventricular dysfunction, or previous embolic events.

1% to 2% per year, and death of 0.2% to 0.5% per year. The bleeding risk is 5% to 6% in patients aged ≥ 70 years. The target international normalized ratio (INR) is between 2.0 and 3.0 for mechanical valves (tilting disk and bileaflet) in the aortic position and 2.5 and 3.5 for mechanical valves in the mitral position. Patient-related risk factors for thromboembolism are older age, atrial fibrillation, and LV dysfunction.

- b. **Bioprosthetic valves.** The need for anticoagulation in bioprosthetic valves is **controversial and is not evidence based**. The risk of embolism is greatest in the early postoperative period, declines after 3 months, and is greater for mitral (7%) than for aortic valves (3%). A reasonable approach is to anticoagulate patients with a **mitral** bioprosthesis for 3 months and then change to aspirin, 325 mg daily. Patients with **aortic prostheses** should receive aspirin, 81 mg daily, for at least 3 months unless there is another reason for anticoagulation. **Patients with prior embolic events, atrial fibrillation, or LV dysfunction should be anticoagulated for the long term.**
2. **Management of anticoagulation in patients with prosthetic valves undergoing noncardiac surgery.** Although the risk of thromboembolism increases when anticoagulant therapy is briefly discontinued, the decision to suspend therapy should be individualized.
 - a. For **major procedures** in which substantial blood loss is expected, **warfarin should be discontinued at least 3 days prior to the procedure** to achieve an INR of 1.6 or less. Hospital admission for **intravenous heparin administration** is often recommended for patients with **caged ball prosthetic valves, atrial fibrillation, left atrial thrombus, severe LV dysfunction, or previous embolization**. Postoperatively, intravenous heparin therapy should be **resumed when it is considered safe and continued until therapeutic anticoagulation is achieved with warfarin**. Low-molecular-weight heparin (LMWH) may be considered for patients with prosthetic valves as bridge therapy.
 - b. For **minor procedures** (e.g., dental extraction) where blood loss is minimal, anticoagulation can be continued.
3. **Pregnancy** (see Chapter 38). Pregnant women have an increased incidence of thromboembolic complications. The use of warfarin through the entire course of pregnancy is associated with warfarin embryopathy in as many as 6.4% of live births. Given its teratogenic effects, **warfarin should be discontinued (at least between 6 and 12 weeks of the pregnancy) when pregnancy is considered or detected during the first trimester**. Subcutaneous heparin 17,500 to 20,000 U every 12 hours with a target-activated partial thromboplastin time of 1.5 to 2.0 times the control 6 hours after injection should be administered until at least between 6 and 12 weeks of pregnancy, at which time warfarin may be resumed and continued until the middle third trimester. Subcutaneous heparin 5,000 U is then administered twice a day until delivery. Low-dose aspirin can be used in conjunction with anticoagulant therapy for women at higher risk for thromboembolism. LMWH or unfractionated heparin may be considered as an alternative for the entire course of the pregnancy. With LMWH, the anti-Xa levels should be monitored to ensure therapeutic efficacy.

II. ASSESSMENT OF PROSTHETIC VALVES

A. Clinical presentation. The clinical presentations of prosthetic valve dysfunction can vary substantially. A discussion of the various entities is detailed in Section III.

1. **History.** This should include a thorough cardiovascular review in addition to questions pertinent to the function of the prosthesis.
 - a. The **indication** for placement of valve prosthesis, **position** of implantation, **type** of prosthesis, and the **year of implantation** should be elicited. The

model and size of the prosthesis can be verified by the identification card provided by the manufacturer.

- b. Other important questions involve **compliance with the anticoagulation regimen**, previous **endocarditis**, **thromboembolism**, **fever**, and perceived **change in the quality of the valvular click**.

2. Physical findings

- a. The physical examination may be remarkable for a **new murmur**, **muffled prosthetic valve sounds**, or **evidence of embolic events**.
- b. Prosthetic valves are associated with **distinct auscultatory events caused by prosthesis motion or altered flow patterns**. The prosthesis sounds may mask the normal heart sounds; significant valvular dysfunction may occur without audible changes. However, familiarity with the normal auscultatory findings in the prosthetic valve examination can provide valuable clues on prosthesis dysfunction prior to the more definitive imaging examination. Figure 18.3 summarizes the acoustic characteristics of common valve prostheses.

B. Laboratory examination and diagnostic testing. The diagnosis of structural valve degeneration relies predominantly on echocardiographic findings, which can often identify degeneration prior to the onset of symptoms.

1. **Two-dimensional echocardiography.** Echocardiography of prosthetic heart valves is more demanding, both to perform and to interpret, compared with the assessment of native valves. By their design, almost all replacement valves are obstructive compared with normal native valves. The degree of obstruction varies with the type and size of the valve. Thus, it may be difficult to differentiate obstructive hemodynamics due to valve design from those of mild obstruction observed with pathologic changes and from prosthesis–patient mismatch. Most

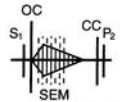
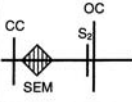
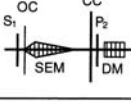
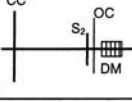
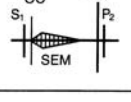
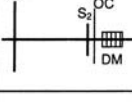
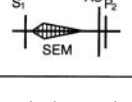
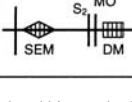
Type of valve	Aortic prosthesis		Mitral prosthesis	
	Normal findings	Abnormal findings	Normal findings	Abnormal findings
Caged ball (Starr-Edwards)		Aortic diastolic murmur Decreased intensity of opening or closing click		Low-frequency apical diastolic murmur High-frequency holosystolic murmur
Single tilting disk (Björk-Shiley or Medtronic-Hall)		Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Bileaflet tilting disk (St. Jude Medical)		Aortic diastolic murmur Decreased intensity of closing click		High-frequency holosystolic murmur Decreased intensity of closing click
Heterograft bioprosthesis (Hancock or Carpentier-Edwards)		Aortic diastolic murmur		High-frequency holosystolic murmur

FIGURE 18.3 Acoustic characteristics of various mechanical and bioprosthetic valves. (From Vongpatanasin W, Hillis LD, Lange RA. Prosthetic heart valves. *N Engl J Med*. 1996;335:410, with permission from the Massachusetts Medical Society.)

mechanical valves and many biologic valves are associated with trivial or mild transprosthetic regurgitation. The pattern of this “physiologic” regurgitation varies with the design of the replacement valve. Last, because of shielding and artifacts, insonation of the valve, particularly of regurgitant jets associated with the valve, may be difficult.

The interrogation of the prosthetic valve requires a thorough evaluation of the native structures and a systematic approach to the following: prosthetic apparatus, peak and mean gradient, and regurgitant flow. Typically, **TEE** is performed to evaluate **patients whose disease is symptomatic or who are suspected of having endocarditis**. The two-dimensional assessment of prosthetic valves is similar to that of the native valve but is **limited by reverberation artifacts and acoustic shadowing**. In general, echocardiographic evaluation should be done to assess the following:

- a. **Occluders and leaflets.** Failure of the leaflet or occluder to open or coapt properly may result from pannus ingrowth (see Section III.H), **thrombus formation** (see Section III.E), or **calcification of bioprosthetic leaflets**. Imaging of leaflets and occluders may be suboptimal with transthoracic echocardiography (TTE). Multipane TEE provides higher temporal and spatial resolution of the prosthesis than TTE and may allow measurement of valve area and mobility. Furthermore, use of real-time biplane imaging can enhance the diagnostic accuracy by providing simultaneous orthogonal imaging planes. Although the aortic prosthesis is less well visualized relative to the mitral prosthesis, TEE still provides a better visual inspection of the posterior aspect of the prosthesis and perivalvular structures than TTE. From 0° to 90° in the lower esophageal position, various aspects of the **mitral prosthesis** can be visualized. The mitral prosthesis can be imaged in cross-sectional view from the transgastric window. Mechanical valve leaflets in the aortic position can be challenging to assess, especially when there are two mechanical valves.
 - b. **Sewing ring.** The orientation of the prosthetic valve in the annulus can be variable; however, **excessive motion** (“rocking”) of the sewing ring is consistent with **dehiscence of the prosthesis**. Concomitant paravalvular regurgitation can be commonly identified with the use of color Doppler mapping. **Furthermore, adjacent echolucent structures** identified in the evaluation of endocarditis may represent abscess, fistula, or pseudoaneurysm. In general, **flow into an adjacent echolucent space is pathologic**. This may involve any portion of the annulus or the mitral–aortic intervalvular fibrosa.
 - c. **Three-dimensional echocardiography.** Three-dimensional echocardiography is increasingly useful in the evaluation of prosthetic valves, as it allows improved display of the complex structures involved especially when used with TEE. Occluder motion and the sewing ring are often well evaluated, and the precise location of an abnormality relative to the sewing ring may be optimally demonstrated.
2. **Doppler evaluation.** Doppler evaluation complements the two-dimensional examination and provides a **reliable indirect assessment of the prosthetic valve performance**. Color Doppler is useful in assessing regions of high velocity, proximal flow convergence, and regurgitant jets, whether they are valvular or perivalvular. Pulsed-wave and continuous-wave Doppler are used to assess transvalvular gradients, from which effective valve areas can be derived.
- a. **Imaging planes for TTE.** Prosthetic mitral and aortic regurgitation can be visualized in the **parasternal long- and short-axis views**. Acoustic shadowing from the aortic and mitral prosthesis can interfere with the color Doppler display in the proximal portion of the aortic and mitral regurgitant jets. The apical views allow assessment of transvalvular pressure gradients but may

underestimate the size of the mitral regurgitant jets due to acoustic shadowing. Pulmonary vein flows may not be available for the same reason. **Prosthetic aortic regurgitation** can be characterized from the **apical window**.

- b. **Imaging planes for TEE.** At 40° from the upper esophageal position (cross-sectional view), the origin of the aortic regurgitant jet (intravalvular or perivalvular) can be identified. The extent of the aortic regurgitant jet into the LV cavity with color Doppler can be visualized at 120°. Advancing the probe to the lower esophagus at 0° brings forth the four-chamber view, which allows unimpeded visualization of the mitral regurgitant jet and measurement of transmitral gradients. Color Doppler interrogation of the medial and lateral aspects of the mitral prosthesis can be performed by increasing the array toward 90° while rotating and advancing or pulling back the probe. Continuous-wave Doppler is used to measure the peak velocity across the prosthesis.

- (1) Continuous-wave Doppler evaluation of the **aortic valve** may be performed at the lower esophageal level using the pinch maneuver (simultaneous ante- and right lateral flexion of the probe). Inserting the probe into the stomach at 5° to 10° with the probe anteflexed allows visualization of the origin of the mitral regurgitant jet. At 90° to 110°, continuous-wave Doppler evaluation of the aortic valve may be performed by left lateral flexion of the probe. Advancing the probe further to the deep transgastric view at 0° with anteflexion also brings the aortic valve in line for Doppler interrogation.

- (2) Continuous-wave Doppler can also be used to assess **mechanical prosthetic regurgitation**. Advantages of continuous-wave Doppler include excellent temporal resolution to allow identification of specific periods in the cardiac cycle and the ability to indicate the severity of a regurgitant jet by its signal intensity. Using two-dimensional or color-flow imaging to guide, continuous-wave Doppler allows interrogation of different parts of the prosthesis and can help to detect eccentric jets. Color Doppler is useful if a view can be obtained where the ultrasound beam can enter the chamber receiving the regurgitant flow without traversing the prosthetic valve.

C. Normal Doppler findings

1. **Prosthetic valve clicks.** The opening and closure of mechanical valve leaflets create a brief intense Doppler signal that appears as a narrow band on the spectral display.
2. **Prosthetic valve velocities/pressure gradients.** The systolic spectral Doppler contour is frequently triangular, with an earlier systolic peak velocity and a higher peak gradient than that of the mean gradient. The expected normal velocities and pressure gradients for commonly used prosthetic valves are shown in Table 18.5. However, there is a large variability in these numbers depending on flow and other factors. Therefore, a postoperative baseline study, usually before hospital discharge, is indicated for patients with prosthetic valves.
3. **Physiologic prosthetic valve regurgitation.** Many prosthetic valves have regurgitant flow characterized by a uniform color without aliasing. For a mechanical prosthesis, the physiologic prosthetic regurgitant flow typically has a regurgitant jet area of < 2 cm² and jet length of < 2.5 cm in the mitral position and a jet area of < 1 cm² and jet length of < 1.5 cm in the aortic position. **Most tissue valves exhibit minor regurgitant flow (closure volume) early after implantation.**
4. **Assessment of prosthetic valve dysfunction.** Loss of prosthetic valve clicks is a sensitive marker for prosthesis dysfunction.
 - a. **Prosthetic valve stenosis**

TABLE 18.5 Normal Doppler Values of Prosthetic Valves

Prosthetic valve	Peak velocity (m/s)	Mean gradient (mm Hg)
Aortic position		
Starr-Edwards	3.1 ± 0.5	24 ± 4
Björk-Shiley	2.5 ± 0.6	14 ± 5
St. Jude	3.0 ± 0.8	11 ± 6
Medtronic-Hall	2.6 ± 0.3	12 ± 3
Aortic homograft	0.8 ± 0.4	7 ± 3
Hancock	2.4 ± 0.4	11 ± 2
Carpentier-Edwards	2.4 ± 0.5	14 ± 6
Mitral position		
Starr-Edwards	1.8 ± 0.4	5 ± 2
Björk-Shiley	1.6 ± 0.3	5 ± 2
St. Jude	1.6 ± 0.3	5 ± 2
Medtronic-Hall	1.7 ± 0.3	3 ± 1
Hancock	1.5 ± 0.3	4 ± 2
Carpentier-Edwards	1.8 ± 0.2	7 ± 2

Modified from Nottestad SY, Zabalgoitia M. Echocardiographic recognition and quantitation of prosthetic valve dysfunction. In: Otto CM, ed. *The Practice of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1997:803.

- (1) **Transvalvular gradients.** Assessment of transvalvular gradients is the mainstay of the Doppler evaluation. **Each prosthetic valve is inherently stenotic and thus has a higher than normal peak velocity across it.** The continuous-wave Doppler gradient across the prosthesis obtained within weeks following implantation serves as a control for subsequent evaluations. High gradients may also be obtained in non-obstructive situations, such as high-output states, tachycardia, anemia, severe prosthetic leaks, or the pressure recovery phenomenon. Pressure recovery occurs secondary to flow acceleration through a narrowed orifice, especially with the mechanical bileaflet prosthesis in the aortic position. With this, the highest pressure measured through the prosthesis by Doppler overestimates the true pressure gradient by approximately one-third. With **prosthetic valve stenosis, pressure recovery becomes less evident.**
- (2) **Valve area calculations.** Calculation of orifice area in prosthetic valves is difficult given the complexity of the orifice (struts/disks and so forth), especially in mechanical prostheses. The following methods have been used to approximate orifice area:
 - (a) **Continuity equation.** The continuity equation can be used to estimate the functional orifice area of prosthetic aortic and mitral valves. For calculation of the prosthetic valve area in the aortic position,

$$\text{Area}_{\text{aortic prosthesis}} = (\text{diameter}_{\text{sewing ring}})^2 \times 0.785 \text{TVI}_{\text{LVOT}} / \text{TVI}_{\text{aortic prosthesis}}$$

where TVI is time–velocity integral and LVOT is left ventricular out-flow tract.

The LVOT diameter is replaced by the sewing ring inner diameter in the equation. The aortic prosthesis TVI is determined from continuous-wave Doppler velocity through the prosthesis. LVOT TVI is determined by pulsed-wave Doppler. Mitral valve prosthesis TVI is determined from continuous-wave Doppler. For the mitral position,

$$\text{Area} = (\text{LVOT diameter})^2 \times 0.785 \times \text{TVI}_{\text{LVOT}} / \text{TVI}_{\text{mitral prosthesis}}$$

- (3) **Pressure half-time (PHT).** For a mitral valve prosthesis, the PHT method is useful for assessing prosthetic valvular stenosis. The empirical constant of 220 provides a reasonable approximation for mechanical prosthetic mitral valve area. The PHT method can also determine whether increased velocity is secondary to increased flow or to obstruction. If the peak velocity is increased but the PHT is not prolonged, then the increased velocity is most likely due to increased forward flow. However, PHT may overestimate the area of the mitral prosthesis. Also if there is concomitant more than mild aortic regurgitation, estimation of prosthetic mitral valve area will not be accurate by PHT method.
- (4) **Dimensionless index. The LVOT and aortic valve prosthesis velocity ratio is possibly the most helpful index for the evaluation of prosthetic valve stenosis,** particularly when the valve size is not known. The higher the index, the larger the EOA, and vice versa. A value ≤ 0.25 suggests prosthesis stenosis:

$$\text{Dimensionless index} = \text{velocity}_{\text{LVOT}} / \text{velocity}_{\text{aortic prosthesis}}$$

- (b) **Pathologic prosthetic valve regurgitation.** The pathologic flow disturbance is **larger and wider than that seen with physiologic regurgitation.** Its **severity can be reliably quantified by TEE,** which can best identify periprosthetic regurgitation. Pathologic regurgitation may be related to a scarred/calcified annulus, with disruption of the sutures securing the valve or a perivalvular abscess with adjacent tissue destruction. Single or multiple jets may be present.
 - (1) Severe mitral prosthetic regurgitation is suggested by increased peak early diastolic velocity (≥ 2.5 m/s) and normal mitral inflow PHT (≤ 150 m/s) (see Chapter 16).
 - (2) Severe aortic regurgitation is usually present when the PHT ≤ 250 milliseconds or when flow reversal is detected in the descending aorta (see Chapter 15).
5. **Cinefluoroscopy.** Cinefluoroscopy is useful for assessing **mechanical prosthetic valves.** The image intensifier is moved to a position with x-rays parallel to the valve ring plane to determine the occluder's excursions in a caged valve. Despite the radiolucency of pyrolytic carbon disk valves, the opening angle can be measured from positioning the image intensifier parallel to the plane of the open leaflets. **The mitral prosthesis is best visualized from the right anterior oblique (RAO) cranial projections. The aortic prosthesis can be viewed from RAO caudal or left anterior oblique cranial projection.**
 - a. Diminished motion of the disks suggests valve obstruction, whereas excessive rocking of the base ring (i.e., 7° for aortic prosthesis and 11° for mitral prosthesis) suggests partial dehiscence of the valve.
 - b. In the setting of **suspected strut fracture in a Björk-Shiley valve,** cinefluoroscopy evaluation of the prosthesis is best performed with the tunnel view

profile. Increased incidence of strut fracture has been noted in patients with an opening angle of 70° or more.

6. Cardiac catheterization

- a. **Invasive assessment** of the left ventricle can be performed safely in patients with bioprosthetic aortic valves. However, catheter-based evaluation of the mechanical aortic valve must be performed with a transseptal technique in patients with a mechanical prosthesis. It may be necessary for accurate measurement of the prosthetic mitral valve gradient, as catheter-based assessment overestimates the mitral valve gradient because of a dampening of the pressure contour and intrinsic delay in the pulmonary capillary wedge tracing.
- b. **Never cross the following prosthetic valves:**
 - (1) Single or bileaflet tilting disk prosthesis
 - (2) Caged disk prosthesis
 - (3) Caged ball prosthesis
7. **Magnetic resonance imaging** can be performed safely in patients with most prosthetic valves, as they are not ferromagnetic. It can identify **prosthetic regurgitation, periprosthetic fistulas, and abscess**. Prosthetic valves cause **imaging artifacts**, which preclude assessment of the leaflets of the prosthetic valve; however, dedicated sequences can provide information about **blood flow velocities** and **regurgitant jets**.
8. **Multislice** gated cardiac CT with retrospective image acquisition also allows adequate evaluation of leaflet motion in mechanical valves using multiplanar reformatting and reconstruction to view the valve motion in any selected plane. The utility of this method over conventional fluoroscopy remains to be evaluated. One particular limitation compared with cinefluoroscopy is the lower temporal and spatial resolution of CT as well as the need for potentially higher doses of ionizing radiation. However, it can be particularly useful in patients with more than one mechanical valve prosthesis, in which echocardiography can be difficult due to artifacts.

III. VALVE DYSFUNCTION AND COMPLICATIONS RELATED TO PROSTHETIC VALVES

- A. **Atrial fibrillation.** Up to 50% of patients undergoing valve surgery experience postoperative atrial fibrillation. Management of atrial fibrillation is discussed in Chapter 24.
 1. In **patients without a previous history** of atrial fibrillation, the **arrhythmia is often self-limited**.
 2. For patients with **persistent atrial fibrillation beyond 24 hours, anticoagulation, direct current cardioversion, and a short course of antiarrhythmic therapy** are warranted.
 3. β -Blockade or amiodarone prophylaxis has been found to reduce the incidence of postsurgical atrial fibrillation.
- B. **Conduction disturbances.** High-grade heart block requiring permanent pacemaker implantation has been described in 2% to 3% of patients after valve replacement and 8% following repeat valve surgery. It is caused by trauma to the bundle of His or from postoperative edema of the periannular tissue. Aortic or mitral annular calcification, preoperative conduction disturbance, advanced age, infectious endocarditis, and tricuspid valve surgery are associated with higher rates of postoperative conduction abnormalities, leading to permanent pacemaker implantation. As mentioned before, the higher profile of Medtronic's self-expandable CoreValve ReValving system has been associated with higher rates (up to 25%) of complete heart block requiring permanent pacemaker implant.
- C. **Endocarditis.** Approximately 3% to 6% of patients with prosthetic heart valves will experience prosthetic valve endocarditis. Prosthetic valve endocarditis is typically

associated with large vegetations, since microorganisms are sheltered from the host defense mechanisms.

1. Early prosthetic valve endocarditis (< 60 days following implantation) is typically caused by *Staphylococcus epidermidis*. The clinical course is often fulminant, with high mortality rates ranging from 20% to 70%.
 2. Late prosthetic valve endocarditis occurs most commonly in patients with multiple prostheses and bioprosthetic valves, especially in the aortic position. Its clinical course resembles that of native valve endocarditis. Streptococci are the most common infectious agents, followed by gram-negative bacteria, enterococci, and *S. epidermidis*.
 3. TEE is the imaging modality of choice, with sensitivity of 95% and specificity of 90% in diagnosis. It is also useful in detecting complications including abscess, tissue invasion, dehiscence, and fistula formation and monitoring the efficacy of medical therapy.
 4. **Therapy.** The mortality of patients managed with antibiotics alone is 61% versus 38% for those having valve replacement. (See Chapter 19 for more information on diagnosis, management, and antibiotic prophylaxis for endocarditis.)
 - a. **Medical therapy.** Medical cure of prosthetic valve endocarditis caused by **staphylococci, gram-negative organisms, or fungi is rare. Streptococcal prosthetic valve endocarditis responds to medical therapy alone in 50% of cases.** Patients with mechanical prosthetic valve endocarditis should **continue to receive anticoagulation.** In the absence of anticoagulation, prosthetic valve endocarditis is associated with up to 50% incidence of stroke. Continuing anticoagulation for patients with prosthetic valve endocarditis is associated with a 10% incidence of cerebral embolization. There is no conclusive evidence for increased hemorrhage with warfarin in patients with prosthetic valve endocarditis. Careful surveillance of medically managed patients with prosthetic endocarditis is essential and should involve an infectious diseases consultant, multiple repeat cultures after the cessation of antibiotic treatment, and follow-up with TEE when needed. A high index of suspicion should be maintained for the presence of residual infection, and surgical reevaluation should be considered if medical treatment fails.
 - b. **Surgical therapy.** Valve replacement surgery is indicated in the setting of
 - (1) persistent bacteremia despite intravenous antibiotics
 - (2) tissue invasion or fistula formation
 - (3) recurrent embolization
 - (4) fungal infection
 - (5) prosthesis dehiscence or obstruction
 - (6) new or worsening heart block
 - (7) **new-onset or worsening** congestive heart failure
- D. **Hemolysis.** Subclinical hemolysis is present in many patients with mechanical valves but **rarely results in significant anemia.**
1. **Pathophysiology and etiology.** Clinical hemolysis occurs in 6% to 15% of patients with **caged ball valves** but is uncommon with normal bioprosthetic or tilting disk valves. Clinical hemolysis is also associated with **multiple prosthetic valves, small prostheses, periprosthetic leaks, and prosthetic valve endocarditis.** Mechanisms involved in the generation of hemolysis include high shear stress or turbulence across the prosthesis, interaction with foreign surfaces such as cloth, and rapid deceleration of erythrocytes following collision with adjoining structures (e.g., struts or cardiac walls).
 2. **Laboratory examination and diagnostic testing**
 - a. Diagnosis is made by **elevated lactate dehydrogenase, reticulocyte count, unconjugated bilirubin, urinary haptoglobin,** and presence of **schistocytes on blood smear.**

- b. Echocardiographic findings consistent with mechanical hemolysis include **abnormal rocking of the prosthesis or regurgitant jets of high shear stress** (e.g., eccentric or periprosthetic regurgitant jets or those impacting a solid surface such as the left atrial appendage or sewing ring).
3. **Therapy**
- a. **Medical therapy.** Mild hemolytic anemia can be managed with **iron, folic acid supplement, erythropoietin stimulants and, if needed, blood transfusion.** **β-Blockade and blood pressure control** may reduce the severity of hemolysis. Paradoxically, treatment of the anemia may reduce the degree of hemolysis by limiting the need for high flow through the defective valve.
 - b. **Surgical therapy.** Repair of perivalvular leaks or valve replacement is indicated in **patients with severe hemolysis requiring repeated transfusions or in those with congestive heart failure.** Increasingly, however, it is possible to reduce focal paravalvular leaks percutaneously with the use of coils or other occluders. Percutaneous approaches are not feasible with extensive dehiscence or where there is active infection.
- E. **Thrombosis.** The annual incidence of mechanical prosthetic valve thrombosis is 0.2% to 1.8%. The incidence is highest in the tricuspid position, followed by the mitral and then the aortic position. Thrombus is suspected in patients with **acute onset of symptoms, embolic event, or inadequate anticoagulation.** Thrombosis at bioprostheses is uncommon but may occur in low-flow or prothrombotic states.
- 1. **Laboratory examination and diagnostic testing.** TEE is the most widely used diagnostic technique, although cinefluoroscopy can be used to document restriction in occluder mobility. Three-dimensional TEE may be of particular value in some instances in outlining the nature of the obstruction. No imaging modality, however, can clearly differentiate thrombus from pannus (see Section III.H). Frequently they coexist. Comparison with previous studies is crucial to determine temporal changes. Although sometimes differentiation of thrombus versus pannus can be difficult, a few things argue more in favor of pannus such as location (aortic > mitral valve), duration since valve implantation, subacute/chronic course, symmetrical involvement, location of thickening (pannus is usually annular, whereas thrombus is most of the times attached to the valve ring). Subtherapeutic anticoagulation over an extended period increases the likelihood of thrombus. Echocardiographic features suggestive of thrombus include soft, irregular, or mobile mass.
 - 2. **Therapy.** The valve type or suspected duration of valve thrombosis does not influence the indications for treatment, although location of prosthetic valve does.
 - a. **Priority of therapy**
 - (1) Heparin is typically initiated early in the course of evaluation.
 - (2) Warfarin is continued unless surgery is planned.
 - (3) TTE, TEE, or cinefluoroscopy should be performed at 24 hours and, if the thrombus is still present, should be repeated serially.
 - b. **Medical therapy**
 - (1) Fibrinolytic therapy is considered the treatment of choice for **right-sided prosthetic valve thrombosis** because the consequences of distal embolization are less severe than in left-sided prosthesis. Streptokinase and urokinase are the most commonly used agents. Fibrinolytic therapy has an initial success rate of 82%, overall thromboembolism rate of 12%, and a 5% incidence of major bleeding episodes. For left-sided valves, there is a similarly high success rate (82%) with fibrinolytic therapy; however, the associated risks of death (10%) or systemic embolism (12.5%) are high. Thrombolysis should be considered for left-sided valves in patients with contraindications to surgery. Thrombolysis may be a reasonable alternative

to surgery for mitral or aortic prosthetic valve thrombosis in patients with a small thrombus burden, particularly if there is hemodynamic compromise and/or multiple comorbidities increasing the surgical risk.

- (a) The classical regimen for **streptokinase** is a 500,000 IU bolus given over 20 minutes, followed by an infusion of 1.5 million IU infused over 10 hours.
 - (b) **rtPA (recombinant tissue plasminogen activator) 10 mg bolus followed by 90 mg an hour for 9 hours.**
 - (c) Thrombolysis should be stopped if there is no hemodynamic improvement after 24 to 72 hours. TEE is useful in assessment of progress.
 - (d) Following successful thrombolysis, close **follow-up of anticoagulation along with serial Doppler echocardiography** on an individual basis is recommended.
- (2) Anticoagulation with heparin and warfarin is generally recommended for **small thrombus** (≤ 5 mm). The regimen consists of intravenous heparin followed by subcutaneous heparin 17,000 U twice a day and warfarin (INR 2.5 to 3.5) for up to 3 months.
- c. **Surgical approach.** The lowest surgical mortality reported has been approximately 5%. The risk profile of the individual patient must be balanced against the expertise and experience at each center.
- (1) Valve replacement and debridement are generally performed for **left-sided prosthetic valve thrombosis**, unless the thrombus is small or the patient has a prohibitive surgical risk.
 - (2) Surgery is also indicated in the case of **unsuccessful thrombolysis** 24 hours following discontinuation of the infusion.
- F. **Dehiscence.** Detachment of the sewing ring from the annulus may occur in the early postoperative period because of poor surgical techniques, excessive annular calcification, chronic steroid use, fragility of the annular tissue (particularly following prior valve operations), or infection. Late dehiscence occurs mainly from infectious endocarditis. **Abnormal rocking of the prosthesis** on echocardiography or cine-fluoroscopy is an **indication for urgent surgery**. Some rocking of a mitral prosthesis may occur normally with preservation of the mitral valve apparatus.
- G. **Patient–prosthesis mismatch.** All prosthetic valves, with the exception of stentless aortic homografts, have effective orifices that are smaller than those of native valves. There is an **inherent pressure gradient and relative stenosis with each prosthesis**. Occasionally, when an inappropriately small prosthesis is placed, the **ensuing low output may cause symptoms**. Patient–prosthesis mismatch should be considered mild if indexed valve EOA is < 0.85 cm²/m², moderate if > 0.65 cm²/m² but ≤ 0.85 cm²/m², or severe if ≥ 0.65 cm²/m². The impact and prevalence of patient–prosthesis mismatch are controversial. Depending on the definition and surgical series used, this mismatch may occur between 20% and 70% of cases after aortic valve replacement. It has been shown in some series to be associated with worse hemodynamic function, less regression of LV hypertrophy, more cardiac events, and lower survival, although others question its importance. Unlike most of the other risk factors, patient–prosthesis mismatch can be avoided or its severity can be more or less reduced by putting in place a prevention strategy at the time of the operation. **It is rare that patient–prosthesis mismatch occurs to a degree that surgical explantation is necessary.** Some important points to consider:
1. The projected indexed EOA should be systematically calculated at the time of the operation to estimate the risk of patient–prosthesis mismatch.
 2. In a patient with a **small annulus, a hemodynamically favorable prosthesis** like a stentless bioprosthesis, aortic homograft, or a tilting disk valve is preferred. Alternatively, the aortic annulus may be enlarged surgically in order to accommodate a prosthesis of acceptable size.

3. Aortic prostheses < 21 mm in diameter are not recommended for a large or physically active patient.
 4. Young patients in particular, as well as those with poor LV function and/or severe LV hypertrophy, are more vulnerable to patient–prosthesis mismatch.
- H. Pannus formation.** Valve obstruction occurs in up to 5% of mechanical valves per year. Valve thrombosis and pannus formation are responsible for the majority of mechanical prosthesis obstructions. Frequently, thrombus coexists with pannus. **Little is known about the causes** of fibroblastic proliferation in pannus formation. Foreign body reactions to the prosthesis, inadequate anticoagulation, endocarditis, and blood flow turbulence in the mitral position have been implicated as potential causes. Pannus formation begins around the annulus of the valve and is more common in aortic than in mitral valve prostheses. A subacute presentation of fatigue or dyspnea in a patient who is well anticoagulated can suggest pannus formation. **TEE and/or cinefluoroscopy is generally required** to identify the cause of prosthetic valve obstruction.
1. **Embolitic stroke.** Following an embolic stroke, the risk of recurrent stroke is approximately 1% per day for the first 2 weeks.
 1. If no evidence of hemorrhage is detected on CT scan at 24 to 48 hours, **intravenous heparin** should be administered after a small to moderate embolic stroke. **Maintaining anticoagulation** reduces the risk of recurrent stroke to one-third but **carries an increased risk of hemorrhagic transformation** of 8% to 24%, particularly during the first 48 hours.
 2. In patients with **larger infarcts, anticoagulation should be withheld for 5 to 7 days.**
 3. Anticoagulation is withheld for 1 to 2 weeks in the setting of **hemorrhagic transformation.**
 4. **Aspirin or clopidogrel** may be needed in the event of recurrent strokes, despite adequate anticoagulation.
 5. Rarely, **reoperation with placement of a tissue valve** is needed for recurrent embolization.
 - J. Mechanical failure**
 1. Failure of **bioprostheses** is expected as the valves age. This may manifest as stenosis, regurgitation, or a combination and is usually due to the deposition of calcium on the leaflets. The onset of mechanical failure is usually gradual. Leaflet tears may produce a sudden clinical deterioration with the onset of severe regurgitation. Bioprosthetic deterioration is managed expectantly with increasing frequency of evaluation as the valve ages and deterioration becomes more evident clinically and on echo. Indications for reoperation are similar to those for native valve lesions, although the threshold to reoperate is somewhat higher, given the greater mortality and morbidity associated with reoperation.
 2. Failure of the current generation of **mechanical prostheses** is rare but may precipitate catastrophic hemodynamic compromise. Catastrophic failure occurs when a strut holding the occluder breaks, allowing the occluder to embolize, resulting in overwhelming regurgitation. Strut failure has been reported most commonly with the Björk-Shiley valve and results from fatigue of a metal weld in valves of specific sizes (larger) and valves with year of manufacture 1981 to 1982, especially, in those younger than 50 years at time of implantation. Explantation of those at highest risk has been recommended; in evaluating patients with Björk-Shiley valves, the risk/benefit of explantation versus strut fracture should be determined, based on the excellent published literature on the topic.
 3. In older ball-in-cage prostheses, ball **variance**, a structural deterioration of the occluder, can occur, giving rise to impaired occluder motion, sticking, and thromboembolism. This is rarely seen nowadays with improved prosthetic materials.

ACKNOWLEDGMENTS: *The author thanks Drs. Ron Jacob and Richard Troughton for their previous contributions to this chapter.*

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Infective Endocarditis

I. INTRODUCTION

- A. Infective endocarditis (IE) is **an infection of the cardiac endothelium**, macroscopically seen as vegetations. Despite modern medical and surgical therapy, IE is a serious and life-threatening condition. Mortality rates are 20% to 30% for both native and prosthetic valve endocarditis (PVE) and may be as high as 70% in certain high-risk patients. The clinical diagnosis is based on multiple elements, and **IE is best managed via multidisciplinary collaboration among cardiologists, cardiothoracic surgeons, and infectious disease specialists**.
- B. The incidence of IE has remained constant over the last 30 years, accounting for 1 case per 1,000 hospital admissions. An estimated 10,000 to 15,000 new cases of IE are diagnosed each year in the United States, and the incidence has increased in the elderly and in illicit injection drug users. There has also been an increase in the number of acute cases, prosthetic valve infections, and cases due to gram-negative, rickettsial, chlamydial, fungal, and fastidious organisms.
- C. Risk factors associated with infection include underlying cardiac structural abnormalities, immunosuppressed status, underlying conditions that predispose patients to pacemaker-related infections, prolonged surgery, reoperation, catheter-related bacteremia, and sternal wound infection.

II. CLINICAL PRESENTATION

- A. **Signs and symptoms.** The clinical manifestations of IE are highly variable, ranging from subtle symptoms to fulminant congestive heart failure (CHF) with severe valvular regurgitation. **Acute IE** presents as marked toxicity and progresses to valvular destruction and metastatic infection over several days to weeks. **Subacute IE** evolves over several weeks to months with mild or modest toxicity and rarely causes metastatic infection. The rate of progression depends upon the virulence of the causative organism, the age and underlying health of the patient, and the nature and extent of the underlying valvular disease.
 - 1. The **hallmarks of IE are fever and a new murmur** (> 85%); however, fever may be absent in patients who are elderly, uremic, or immunosuppressed. Murmurs may be absent with right-sided or mural infection or intracardiac device infections.
 - 2. The patient often has nonspecific symptoms of fatigue, weight loss, malaise, chills, night sweats, and/or musculoskeletal aches.
- B. **Physical findings.** A new murmur remains an important finding.
 - 1. CHF occurs in up to 55% of cases and tends to be more common in those with aortic valve disease (75%) than in those with mitral (50%) or tricuspid (20%) valve involvement.
 - 2. Neurologic findings may include clinically apparent cerebral emboli (20%), encephalopathy (10%), mycotic aneurysm leak (< 5%), meningitis, or brain abscess (< 5%).

3. Additional physical findings reflecting **embolic or immune complex phenomena** include mucosal **petechiae** (20% to 40%), **splinter hemorrhages** (subungual dark linear streaks: 10% to 30%), **Osler's nodes** (painful, tender erythematous nodules on the pads of fingers or toes: 10% to 25%), **Janeway lesions** (erythematous, macular, nontender lesions on the fingers, palms, or soles: < 5%), **clubbing** (10% to 20%), **arterial embolism** (peripherally or centrally), **splenomegaly** (30% to 50%), and **Roth's spots** (retinal hemorrhages: < 5%). These classic physical findings are **neither sensitive nor specific** for the diagnosis of IE, and their frequency is continuing to diminish due to a decrease in *Streptococcus viridans* IE and an increase in *Staphylococcus aureus* IE.
4. A formal **fundoscopic examination** should be routine in all patients with suspected or documented IE. It may reveal **chorioretinitis or endophthalmitis**.
5. **Systemic** embolization occurs in 25% to 50% of cases of IE and may mimic acute coronary syndrome (coronary artery emboli), peritonitis (embolization to the spleen, kidney, or bowel), acute stroke (cerebral emboli), and pulmonary embolism (from right-sided IE) or cause a cold extremity with reduced or absent pulse. Septic emboli also cause Janeway lesions.

III. ETIOLOGY

Table 19.1 presents the various etiologic factors.

- A. **Seventy percent to 75% of patients with IE have preexisting cardiac abnormalities. Mitral valve prolapse with regurgitation is the leading condition** underlying IE in adults. Rheumatic heart disease as a substrate for IE is decreasing, with congenital heart disease underlying 10% to 20% of IE cases.
- B. The source of infection can only be identified occasionally (e.g., dental procedures, an infected vascular catheter, or an infected skin lesion). In many patients, there is no history of an antecedent localized infection.
- C. **Native valve endocarditis**
 1. The most common microorganisms that cause native valve IE in adults are streptococcal and staphylococcal organisms (80%). Other important causes

TABLE 19.1 Frequency of Organisms Causing Infective Endocarditis

Organism	NVE (%)	IDU (%)	Early PVE (%)	Late PVE (%)
Streptococci	60	15–25	5	35
Viridans <i>Streptococcus</i>	30–40	5–10	< 5	25
<i>S. bovis</i>	10	< 5	< 5	< 5
Enterococci	10	10	< 5	< 5
Staphylococci	25	50	50	30
Coagulase positive	23	50	20	10
Coagulase negative	< 5	< 5	30	20
Gram-negative (aerobes)	< 5	5	20	10
Fungi	< 5	< 5	10	5
Culture negative	5–10	< 5	< 5	< 5

IDU, intravenous drug use; NVE, native valve endocarditis; PVE, prosthetic valve endocarditis.

Adapted from Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's the Heart*. 11th ed. New York, NY: McGraw Hill; 2004.

include *Streptococcus bovis*, *Enterococcus*, and the HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) group organisms. The HACEK group, accounting for roughly 3% of cases, includes fastidious gram-negative organisms that are normal flora in the upper respiratory tract. *S. bovis* IE is often associated with colonic polyps and colon cancer; as such, a colonoscopy is recommended for these patients.

2. Right-sided IE in injection drug users is usually due to *S. aureus* (60%), with a predilection for normal as well as abnormal cardiac valves. Despite the virulence of this organism, the disease tends to be **less severe** (mortality rates of 2% to 6%) than with left-sided IE. The valve most commonly affected in injection drug users is the tricuspid valve (60% to 70% of cases), followed by the mitral (30% to 40%) and the aortic valves (5% to 10%). More than one valve is involved in 20% of these patients. Septic pulmonary emboli occur in up to 75% of injection drug users with tricuspid IE.
 3. IE from *Pseudomonas aeruginosa* is both **destructive and poorly responsive to antibiotic therapy and thus often necessitates surgical intervention**.
 4. Enterococcal IE is increasing in prevalence. The diagnosis must be considered in patients who have undergone recent genitourinary or obstetric procedures; these patients may not have underlying heart disease.
 5. Other members of the Enterobacteriaceae (*Escherichia coli*, *Salmonella*, *Klebsiella*, *Enterobacter*, *Proteus*, *Serratia*, *Citrobacter*, *Shigella*, and *Yersinia*) are occasionally implicated in IE.
 6. *Streptococcus pneumoniae* accounts for 1% to 3% of native valve IE, and it may present as part of the “**Osler triad**,” which also includes pneumococcal pneumonia and meningitis. Alcoholics are typically affected, and the mortality rate is high (30% to 50%).
 7. The most common congenital heart anomalies predisposing to IE are bicuspid aortic valve, patent ductus arteriosus, ventricular septal defect, coarctation of the aorta, and tetralogy of Fallot. There is **no evidence** that secundum atrial septal defects increase the risk of IE.
 8. *Staphylococcus lugdunensis* is a rare but destructive cause of IE. This organism is a coagulase-negative *Staphylococcus*; however, it differs from other coagulase-negative staphylococci in its aggressive nature and predilection for native valves. *S. lugdunensis* IE portends a high complication and mortality rate without surgical intervention.
- D. PVE accounts for about 10% to 20% of all cases of IE. The greatest risk of infection is in the first 6 months after valve implantation and appears to be **similar in mechanical and bioprosthetic valves**. Recent studies have suggested that infection occurs with similar frequencies at the mitral and aortic positions.
1. PVE occurring within 2 months of surgery (early PVE) is commonly associated with intraoperative contamination and nosocomial infection and this usually implicates **coagulase-negative staphylococci** (30% of cases). The second most common pathogen in early PVE is *S. aureus* (20% of cases).
 2. The microbiology of PVE with an onset of more than 2 months after surgery (late PVE) reflects the pathogens of native valve IE and is most commonly caused by streptococcal species, *S. aureus*, and *Enterococcus*. Coagulase-negative staphylococci cause < 20% of infections in this period. Fungi account for 10% to 15% of late PVE cases and are associated with a higher mortality rate. Among 270 cases of fungal endocarditis reported from 1965 to 1995, 135 (50%) occurred on prosthetic valves. These patients generally lacked an identifiable portal of entry for fungemia. Establishing the diagnosis of fungal PVE can be difficult due to the low yield from blood cultures. Despite aggressive antifungal therapy, these patients remain at risk for the development of PVE months or years later. *Corynebacterium* species and other coryneform bacteria, often called

diphtheroids, are also an important cause of PVE during the first year after surgery (5%). Although they are often blood culture contaminants, diphtheroids in multiple cultures should not be ignored.

- E. Pacemaker/defibrillator endocarditis is increasing in frequency in clinical practice with the burgeoning number of devices being implanted. The incidence of endocarditis following device therapy ranges from 0.2% to 7%. The infection may involve the generator or defibrillator pocket, the electrodes, and valvular or nonvalvular endocardium.
 1. Pacemaker/defibrillator endocarditis occurring within 1 to 2 months of surgery is likely caused by direct intraoperative microbial seeding. Late infection in the pocket produces a thinning of the overlying tissue and ultimately device erosion. The infection may eventually involve the electrodes and ultimately the endocardium. Hematogenous dissemination from distant sites of infection appears to be relatively rare, with the exception of *S. aureus* bacteremia.
 2. The majority of infections in PVE are caused by staphylococci: *S. aureus* and coagulase-negative staphylococci. More than 90% of early infections are caused by coagulase-negative staphylococci, whereas late infections are caused by both *S. aureus* (50%) and coagulase-negative staphylococci (50%). Infection by gram-negative bacilli, enterococci, or fungi is rare.
- F. The incidence of **culture-negative endocarditis** may be as high as 10%. Blood culture-negative endocarditis is defined as endocarditis without positive cultures after inoculation of three blood samples. Cultures can be negative in IE when there is infection with a fastidious bacteria or fungus, the microbiological techniques are inadequate, or there had been administration of antibiotic therapy prior to obtaining blood cultures. The latter reason is the most common cause of culture-negative IE, and the most common causative agents are *Streptococcus* or fastidious organisms such as fungi, HACEK organisms, anaerobes, *Legionella*, *Chlamydia psittaci*, *Coxiella*, *Brucella*, *Bartonella*, *Tropheryma whippelii*, and nutritionally deficient streptococci. *Bartonella henselae* infection is a rare cause of subacute IE, which is associated with exposure to cats. *Coxiella burnetii* causes Q fever and often infects previously damaged valves or prosthetic valves. *T. whippelii* is the cause of Whipple's disease, and this organism can be identified using periodic acid-Schiff staining of macrophages or polymerase chain reaction (PCR). **Nonbacterial endocarditis** (Libman-Sachs, marantic, and antiphospholipid syndrome) should also be considered in cases of culture-negative IE.
- G. Fungal endocarditis (*Candida* and *Aspergillus*) usually occurs in association with **prosthetic valves, indwelling intravascular hardware, immunosuppression, or injection drug use. The most common cause is *Candida* species, but other causes include *Histoplasma* and *Aspergillus*. Fungal IE usually presents with large vegetations that extend into the perivalvular apparatus and embolize into large vessels and therefore requires surgical intervention.**

IV. PATHOPHYSIOLOGY. The first step in the pathogenesis of vegetation is the formation of a **nonbacterial thrombotic endocarditis (NBTE)**, which usually results from endothelial injury followed by focal adherence of platelets and fibrin. Microorganisms circulating in the bloodstream in turn infect this sterile platelet-fibrin nidus.

- A. **Vegetations classically occur along the line of closure of the valve leaflet.** The endothelium may be injured by regurgitant jets, leading to vegetation formation on the atrial surface of incompetent atrioventricular valves or the ventricular surface of incompetent semilunar valves. The foreign body, such as an intracardiac device, is not endothelialized initially and acts as a formation site for platelet-fibrin thrombi.
- B. Bacteremia is the event that converts NBTE to IE when host defenses fail. The foreign material also impairs host defenses, rendering them more difficult to treat.

- C. Vegetations often further impair valvular coaptation or cause perforation or chordal rupture, leading to worsening of regurgitation and CHF. Furthermore, the vegetations may dislodge, causing peripheral septic–nonseptic embolization.
- D. The infection may extend to the surrounding structures, such as the valve ring, the cardiac conduction system, the adjacent myocardium, or the mitral–aortic intravalvular fibrosa. Consequently, conduction defects, abscesses, diverticula, aneurysms, or fistula may develop. Infections involving prosthetic valves commonly invade paravalvular tissue, resulting in abscess formation or valve dehiscence.

V. LABORATORY EXAMINATION

A. Blood tests

1. Laboratory findings often reflect nonspecific acute inflammatory response, manifest as a **modest leukocytosis**, a **normochromic normocytic anemia**, and a slightly increased or decreased **platelet count**. Other laboratory abnormalities may include an **elevated erythrocyte sedimentation rate**, C-reactive protein, rheumatoid factor, and/or a hypergammaglobulinemia. IE may also cause false-positive Venereal Disease Research Laboratory (VDRL) test and Lyme serologic test.
2. Decreased complement and an elevated blood urea nitrogen or creatinine may implicate renal dysfunction from an immune complex glomerulonephritis or drug toxicity.
3. Blood cultures are critical in the diagnosis and management of IE. However, if a patient is acutely ill, **therapy should not be delayed for more than 2 to 3 hours**, as a fulminant infection may be rapidly fatal. In recent reports, cultures were negative in 2% to 7% of cases with established IE, despite the best modern methods.
 - a. If the clinical condition allows, three sets of cultures should be drawn at three different venipuncture sites before empiric antimicrobial therapy is started. Each set should include two flasks, one containing an aerobic medium and the other an anaerobic medium, into which at least **20 cm³** (per tube) of blood should be placed. The HACEK group bacteria are cultured routinely. Fungal cultures should be included when fungal infection is suspected, such as in immunocompromised hosts.
 - b. Intravascular infection leads to constant bacteremia originating from vegetations. Therefore, **it is unnecessary to await the arrival of a fever spike or chills to obtain blood cultures**.
 - c. The laboratory should be alerted if a **culture-negative IE or a fastidious infectious agent** is suspected, as it may be necessary to enhance the culture medium or prolong the incubation period. For example, the HACEK group (see Section **III.C.1**) needs prolonged incubation of up to 21 days. The most common culture-negative IE organisms are *C. burnetii*, *Bartonella* sp., *T. whipplei*, HACEK group bacteria, *Brucella* sp., *Legionella* sp., *Mycoplasma* sp., *Mycobacterium*, and fungi. Serology for *Brucella*, *Legionella*, *Coxiella*, or *Psittacosis* may be revealing. Fastidious organisms can also be identified using PCR in valvular specimens. This technique does not require a culture medium; however, it does require excised valvular tissue. PCR has been shown to have a sensitivity of 41% and a specificity of 100% in recent studies, and thus it may provide important information about the causes of IE that could not be identified by culture. This information may help guide future empiric treatment plans in certain patient populations.
 - d. Special attention should be paid to cultures positive for coagulase-negative staphylococci. *S. lugdunensis* is a coagulase-negative Staphylococcus that rarely causes IE. Unlike other coagulase-negative staphylococci it often affects native valves, is destructive, frequently causes abscesses, and is associated with high mortality without surgical intervention. Thus, in the setting of

high suspicion for IE, cultures positive for coagulase-negative staphylococci should not be disregarded as a contaminant and should be further speciated.

- B. Histologic evaluation.** Histopathology of resected valvular tissues remains the gold standard for the diagnosis of IE. It may demonstrate valvular inflammation, vegetations, and/or specific organisms. Detection of an etiologic agent in the vegetation using special stains or immunohistology can guide the choice of antimicrobial treatment. This is particularly useful in culture-negative IE, such as Q fever, *Bartonella* spp., or *T. whipplei* (Whipple's disease bacillus). **Good communication among cardiologists, surgeons, pathologists, and microbiologists helps ensure accurate diagnosis.**
- C. Urinalysis.** Microhematuria with or without proteinuria may be seen.
- D. Electrocardiography.** All patients with suspected IE should undergo baseline and follow-up electrocardiogram (ECG).
 - 1. ECG may reveal **conduction disturbances** reflecting intramyocardial extension of infection, ranging from a prolonged PR interval to complete heart block (especially with PVE). A **new atrioventricular block** carries a 77% positive predictive value for abscess formation with 42% sensitivity.
 - 2. Myocardial infarction due to embolization of vegetations occurs rarely.
- E.** Chest x-ray may reveal **CHF or pleural effusions**. Right-sided IE may cause **non-specific infiltrates** due to multiple septic pulmonary emboli.

VI. DIAGNOSTIC IMAGING TECHNIQUES

- A. Echocardiography has a key role in both diagnosis and management of IE.** The primary objective is to identify, localize, and characterize valvular vegetations and their effects on cardiac function. Vegetations may occur at intracardiac locations other than valves, such as the site of impact of a high-velocity jet or shunt. A limitation of echocardiography is that vegetations cannot always be distinguished from other noninfectious masses.
 - 1. All patients in whom IE is suspected should undergo baseline transthoracic echocardiography (TTE) to define underlying cardiac abnormalities, to determine the size and location of vegetations, and to explore the possibility of complications (e.g., aortic annular ring abscess). TTE has a low sensitivity for vegetations in IE (29% to 63%) but has close to 100% specificity. However, the finding of morphologically and functionally normal valves on TTE decreases the likelihood of IE. In one series, 96% of patients with normal valves on TTE also had a negative transesophageal echocardiography (TEE).
 - 2. TEE has increased the diagnostic accuracy of IE. If IE is strongly suspected and the TTE is negative, then TEE should be performed because it is more sensitive in detecting vegetations, especially if TTE imaging is difficult. TEE is particularly useful for assessing posterior structures, abscesses, fistulae, perivalvular leaks, small vegetations, right-sided heart structures, masses on intracardiac devices, leaflet perforations, and prosthetic valves. The ability to detect paravalvular abscesses, fistulae, and paraprosthetic leaks has a major impact on management strategy. Intraoperative TEE can be used to evaluate the success of surgical interventions and the need for potential modification of reparative cardiac surgical procedures. A postoperative TTE should also be done as a baseline measure of cardiac anatomy/function for long-term follow-up. Although in most cases a TTE should be the first diagnostic test of choice, in certain circumstances TEE may be the optimal initial test to rule out IE. These include cases that involve *S. aureus* bacteremia, prosthetic valves, prior IE, limited echo windows, and bacteremia due to an organism that is known to commonly cause IE.
 - a.** A negative result on TEE indicates a low likelihood of IE (provided adequate images are available). However, it does not completely rule out the diagnosis. The negative predictive value is > 90%, but false negatives may occur early

in endocarditis or if vegetations are small. Repeat TEE should be considered if clinical suspicion is high. Of note, a negative TEE should never override strong clinical evidence of endocarditis in the diagnosis of PVE.

- b. Myocardial abscesses are more reliably detected with TEE (87% sensitive) than with TTE (28% sensitive). Detection of a perivalvular abscess is essential, as an abscess is a serious complication and a strong indication for surgical intervention.
- c. In the setting of PVE, TEE is superior (82% sensitive) to TTE (36% sensitive) in the detection of vegetations due to acoustic shadowing of prosthetic valves, especially in the mitral and aortic positions. **TEE should be performed if PVE or pacemaker endocarditis is suspected but is not evident on TTE.**
3. Fungal endocarditis tends to cause larger vegetations than bacterial infections, whereas in Q fever vegetations are often absent. Care should be taken to differentiate bacterial vegetations from myxomas, papillary fibroelastomas, rheumatoid nodules, inflammation involving degenerative valvular lesions, Lambli's excrescences, and nonbacterial endocarditis. **It is essential to interpret images in conjunction with clinical data.**
4. One meta-analysis showed that the **risk of embolization in patients with large vegetations (> 10 mm) was nearly three times higher than in patients with no detectable vegetations** or small vegetations. Prolapsing vegetations and involvement of extravalvular structures increase the overall risk of heart failure, embolization, and need for valve replacement. Vegetations that increase in size, despite appropriate therapy, are also more likely to be associated with adverse events requiring surgery.
5. TEE is indicated in patients with suspected pacemaker or defibrillator endocarditis. The sensitivity of TTE for detecting valvular or lead vegetations is 30%, compared with 90% with TEE.
- B. **Cardiac catheterization.** Left heart catheterization with selective coronary angiography is indicated prior to surgical intervention if there is a suspicion of obstructive coronary disease. The abnormal rocking motion of a dehiscence prosthetic valve may be noted on fluoroscopy. Care should be taken to avoid unnecessary coronary angiography or cardiac catheterization in aortic valve endocarditis because of the risk of embolization of vegetations.
- C. **Central nervous system (CNS) imaging.** Computerized tomography (CT), magnetic resonance imaging (MRI), or cerebral angiography should be considered in any patient who has sustained a CNS complication, such as an embolic infarct, intracranial bleed, or mycotic aneurysm, or in the patient with persistent headaches.
- D. **Body imaging.** CT or MRI may be useful in the detection of metastatic infection. The value of CT may increase in the future as spatial resolution improves. **MRI** does not currently have a significant role in assessing cardiac manifestations of IE, owing to intrinsic problems related to temporal resolution.

VII. DUKE CRITERIA. Given the complexity of IE, the diagnosis requires a high index of suspicion. The Duke schema is currently the most sensitive and specific diagnostic set of criteria available. It is particularly useful in diagnosing endocarditis in patients with *S. aureus* bacteremia, those with right-sided endocarditis, and those with negative blood culture results. However, these criteria have not been validated in PVE.

- A. The criteria are divided into **definite** (pathologic or clinical), **possible**, and **rejected** diagnostic groups.
- B. For a **definite pathologic diagnosis**, either (A or B) of the pathologic findings listed in Table 19.2A is sufficient.
- C. For a **definite clinical diagnosis** (Table 19.2B), two major criteria, or one major and three minor, or five minor criteria are needed.

TABLE 19.2A Duke Criteria: Definite Pathologic Diagnosis

- A. Microorganisms, as demonstrated by culture or histology in vegetation
Vegetation that has embolized
Intracardiac abscess
- B. Pathologic lesions
Vegetation or intracardiac abscess present, confirmed by histology showing active endocarditis

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

TABLE 19.2B Duke Criteria: Definite Clinical Diagnosis

Major clinical criteria

1. Positive blood culture results for infective endocarditis
 - A. Typical microorganisms (in two or more cultures)
 - Viridans *Streptococcus*
 - *S. bovis*
 - HACEK group
 - *S. aureus*
 - Community-acquired enterococci, in the absence of a primary focus
 - B. Persistently positive blood culture
 - Recovery of a microorganism consistent with IE from two blood cultures drawn more than 12 h apart

or

 - Recovery of a microorganism consistent with IE from all of three or a majority of four or more separate blood cultures, with the first and last draw at least 1 h apart

or

 - Single positive blood culture for *Coxiella burnetii* or anti-phase 1 IgG antibody titer > 1:800
2. Evidence of endocardial involvement
 - A. Positive echocardiogram
 - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets or on implanted material, in the absence of an alternative anatomic explanation

or

 - Abscess

or

 - New partial dehiscence of prosthetic valve

or
 - B. New valvular regurgitation (increase or change in preexisting murmur not sufficient)

TABLE 19.2B Duke Criteria: Definite Clinical Diagnosis (*Continued*)**Minor clinical criteria**

1. Predisposition:
 - Predisposing heart condition
 - Injection drug use
2. Fever > 38.0° C (100.4° F)
3. Vascular phenomena
 - Major arterial emboli
 - Septic pulmonary infarcts
 - Mycotic aneurysm
 - Intracranial hemorrhage
 - Conjunctival hemorrhages
 - Janeway lesions
4. Immunologic phenomena
 - Glomerulonephritis
 - Osler's nodes
 - Roth's spots
 - Rheumatoid factor
5. Microbiologic evidence
 - Positive blood culture but not meeting major criteria as noted above
 - Serologic evidence of active infection with organism consistent with infective endocarditis

HACEK, *Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*; IE, infective endocarditis.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

- D. The **possible diagnostic** group has findings consistent with IE, including one major criteria and one minor criteria or three minor criteria.
- E. For a **rejected diagnosis**, there is a firm alternative diagnosis for clinical manifestations or resolution of clinical manifestations, with antibiotics for 4 days or less, or no pathologic evidence of IE at surgery or autopsy, after antibiotic therapy for 4 days or less.

VIII. THERAPY. Due to the complexity of IE, a team approach (cardiologist, cardiothoracic surgeon, infectious diseases specialist, and pathologist) in the diagnosis and management of this disease cannot be overemphasized. Effective therapy requires identification of the microbial cause, determination of a bactericidal regimen of proven efficacy, an understanding of the intracardiac pathology of IE and its implications for surgery, and effective management of extracardiac complications.

A. Medical therapy

1. **Principles of therapy.** Antibiotic regimens should be bactericidal and chosen in consultation with an infectious diseases specialist. **Measures of antibiotic effectiveness** include the minimum inhibitory concentration (MIC) of antibiotic required to inhibit growth, the minimum bactericidal concentration (MBC) of an antibiotic required to kill an organism, and the serum bactericidal titer (SBT), which is the highest dilution of a patient's serum that kills 99.9% of an inoculum. The SBT is especially helpful when treating unusual organisms, when using unusual antibiotic regimens, or when treatment is failing. The MIC and MBC are not routinely measured, but currently recommended antimicrobial regimens for specific organisms are based on these values.
 - a. Combination therapy using a β -lactam agent such as penicillin with an aminoglycoside has a synergistic bactericidal effect in streptococcal IE and is also somewhat effective in a subset of patients with staphylococcal IE. However, aminoglycoside resistance represents the most common and grave obstacle to optimal therapy for enterococcal endocarditis.
 - b. A multidrug regimen is recommended for optimal management of staphylococcal PVE. Rifampin has a unique ability to kill staphylococci. However, staphylococci have a relatively high intrinsic mutation rate for the gene controlling the site of rifampin action. Therefore, when large populations of staphylococci are exposed to rifampin, selection of rifampin-resistant organisms is common. Often, antistaphylococcal agent(s) may be administered for 3 to 5 days to reduce the total number of staphylococci before the commencement of rifampin. A multidrug approach (two antibiotics that are known to be active against the staphylococcal isolate in addition to rifampin) may reduce the probability of developing rifampin-resistant subpopulations.
 - c. Renal function is an important consideration when using **aminoglycosides or vancomycin**. These antibiotics should be dosed according to estimated creatinine clearance. The following doses outlined are for normal renal function. A vancomycin dose should not exceed 2 g per 24 hours unless serum levels are monitored.
 - d. Anticoagulation does not prevent embolization related to IE. In fact, **simultaneous treatment with penicillin and heparin increases the risk** of fatal intracerebral hemorrhage. Warfarin may be given safely during the treatment of patients with PVE.
2. Empiric therapy for IE is often started and continued until the etiologic organism is identified and the antibiotic sensitivities are known, especially in cases with hemodynamic compromise. Occasionally, empiric therapy is administered as a therapeutic trial to help confirm a diagnosis. Empiric therapy should cover the most likely pathogens, including staphylococci (both methicillin-sensitive and methicillin-resistant strains), streptococci, and enterococci. Vancomycin plus gentamicin is the recommended empiric regimen in native valve endocarditis, with the addition of rifampin in PVE. Once an etiologic agent is identified, therapy should be narrowed (see Tables 19.3A–F). Unless clinical or epidemiologic clues suggest an etiologic factor, treatment for culture-negative IE is the same.
3. It is important to point out that when initiating therapy for coagulase-negative staphylococcal PVE, the organism should be assumed to be methicillin-resistant until the laboratory definitively excludes this.
4. Antibiotic therapy **after surgery** is discussed in **VIII.B**.
5. Medical therapies for **specific organisms** are summarized in Tables 19.3A–F.
6. **Uncommon causes of IE.** *C. burnetii* IE is treated with doxycycline and rifampin, trimethoprim-sulfamethoxazole, or fluoroquinolones for at least 3 years and requires surgical intervention in cases of prosthetic valve involvement, CHF, or

TABLE 19.3A Therapies for Native Valve Infective Endocarditis due to Penicillin-Susceptible Viridans *Streptococcus* or *S. bovis*

Medication	Dosage	Duration of therapy (wk)
Penicillin G	12–18 million U per 24 h continuously IV or in 4–6 divided doses	4
or		
Ceftriaxone	2 g once daily IV or IM	4
or		
Penicillin G	12–18 million U per 24 h continuously IV or in 6 divided doses	2 ^a
or		
Ceftriaxone <i>plus</i>	2 g once daily IV or IM	2
Gentamicin <i>or</i> if penicillin allergic	3 mg/kg once daily IV or IM	2
Vancomycin	30 mg per 24 h in 2 divided doses	4

IM, intramuscular; IV, intravenous.

^aFor relatively resistant viridans *Streptococcus* or *S. bovis*, or known cardiac or extracardiac abscess, or for those with creatinine clearance < 20 mL/min, penicillin G dosing is extended to 4 weeks.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

TABLE 19.3B Standard Therapies for Susceptible Enterococci, for Resistant and Nutritionally Variant Viridans *Streptococcus* Infective Endocarditis, and for Prosthetic Valve Endocarditis due to Viridans *Streptococcus* or *S. bovis*

Medication	Dosage	Duration of therapy (wk)
Penicillin G	24 million U per 24 h continuously IV or in 4–6 divided doses	6
or		
Ceftriaxone	2 g once daily IV or IM	6
with or without		
Gentamicin	3 mg/kg once daily IV or IM	2–6 ^a
or		
if penicillin allergic, vancomycin	30 mg/kg IV per 24 h in 2 divided doses	6

IM, intramuscular; IV, intravenous.

^aIf penicillin-susceptible strain (minimum inhibitory concentration ≤ 0.12 μ g/mL), duration of gentamicin in combination with ceftriaxone is 2 weeks; if penicillin relatively resistant or fully resistant strain (minimum inhibitory concentration > 0.12 μ g/mL), duration of gentamicin is extended to 6 weeks.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

TABLE 19.3C Therapies for Infective Endocarditis due to Methicillin-Sensitive *Staphylococcus* in the Absence of Prosthetic Material

Medication	Dosage	Duration of therapy
Nafcillin or oxacillin	2 g IV every 4 h	6 wk
<i>plus</i> optional gentamicin	1 mg/kg IV or IM every 8 h	3–5 d
<i>or</i> Cefazolin	2 g IV every 8 h	6 wk
<i>plus</i> optional gentamicin	1 mg/kg IV or IM every 8 h	3–5 d
<i>or</i> if penicillin allergic, vancomycin ^a	30 mg/kg per 24 h in 2 divided doses	6 wk

IM, intramuscular; IV, intravenous.

^aRecommended for methicillin-resistant *Staphylococcus*.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

TABLE 19.3D Therapy for Infective Endocarditis due to Methicillin-Sensitive *Staphylococcus* in the Presence of Prosthetic Material

Medication	Dosage	Duration of therapy (wk)
Nafcillin ^a or oxacillin	2 g IV every 4 h	> 6
<i>plus</i> rifampin	300 mg orally every 8 h	> 6
<i>plus</i> gentamicin	1 mg/kg IV or IM every 8 h	2

IM, intramuscular; IV, intravenous.

^aFor methicillin-resistant *Staphylococcus* or for the penicillin-allergic patient, vancomycin, 30 mg/kg per 24 h IV in two divided doses, is substituted for nafcillin.

refractory infection. *Brucella* IE usually requires surgical intervention in combination with doxycycline and either streptomycin or gentamicin for 8 weeks to 10 months after surgery. *Pseudomonas* IE should be treated with high doses of piperacillin and tobramycin and requires surgical intervention in cases of left-sided infection.

7. **Fungal IE.** When fungal IE is diagnosed, the standard of care involves a **combined medical/surgical approach**.
 - a. The mainstay of antifungal drug therapy is **amphotericin B** with or without **flucytosine** (a synergistic effect).

TABLE 19.3E Therapy for Infective Endocarditis due to HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, and *Kingella*) Microorganisms

Medication	Dosage	Duration of therapy
Ceftriaxone ^a	2 g once daily IV or IM	4
or		
Ampicillin–sulbactam ^a	3 g IV every 6 h	4
or		
Ciprofloxacin	1,000 mg orally once daily or 400 mg IV every 12 h	4

IM, intramuscular; IV, intravenous.

^aThe third-generation cephalosporins or ampicillin–sulbactam therapy should be considered the drugs of choice. Length of therapy for prosthetic valve infective endocarditis should be 6 weeks. A fluoroquinolone should be considered as an alternative agent for patients unable to tolerate β -lactam therapy.

Adapted from Baddour LM, Wilson WR, Bayer AS, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394–434.

TABLE 19.3F Therapy for *Pseudomonas aeruginosa* and Other Gram-Negative Bacilli (Enterobacteriaceae)^a

Extended-spectrum penicillin (ticarcillin or piperacillin)

or

third-generation cephalosporin

or

imipenem

plus aminoglycoside

^aCombination therapy is recommended. The final choice of antibiotic therapy is to be made after sensitivity results are available.

- (1) Amphotericin B is infused in 5% dextrose over 2 to 4 hours at a dose of 0.7 to 1.0 mg/kg daily. Larger doses (1 to 1.5 mg/kg daily) are recommended for the management of PVE caused by *Aspergillus* spp.
- (2) The major toxicity of amphotericin B is **renal dysfunction**. Liposomal preparations may be less nephrotoxic.
- (3) The primary toxicity of flucytosine is **bone marrow suppression**; for this reason, flucytosine blood levels may be useful during therapy.
- b. After 1 to 2 weeks of full-dose amphotericin B therapy, surgery should be performed because effective penetration of the medicine into vegetations is unlikely. Valve replacement becomes necessary in almost all cases of fungal IE.
- c. Long-term oral suppressive therapy with antifungal agents such as fluconazole or itraconazole is commonly recommended to prevent relapse.

B. Surgical therapy (Table 19.4). Surgery is indicated in approximately 25% to 30% of cases during the acute phase of infection and in another 20% to 40% in subsequent or secondary phases. Antibiotic therapy combined with valve replacement and cardiac reconstruction results in higher survival rates and fewer relapses or rehospitalizations and lower late endocarditis-related mortality than do antibiotics alone in patients with complicated IE.

1. The **fundamental principles** of operative procedures for IE involve debridement of infected tissue, removal of all nonviable tissue, reconstruction of the involved area, and restoration of valve competence. There is general consensus for surgical intervention in any of the following situations: refractory CHF due to significant valve dysfunction, native and PVE caused by *S. aureus*, uncontrolled infection, failed antimicrobial therapy with perivalvular extension of infection, most cases of PVE, most cases of fungal IE, and established abscess. Controversial indications include the presence of more than one serious systemic embolic event or one embolus with a large residual vegetation. These indications are not absolute and must be implemented with a careful risk–benefit analysis (see the American College of Cardiology/American Heart Association [ACC/AHA] guidelines for surgical intervention in Table 19.4).
2. CHF (New York Heart Association class III or IV) is the strongest indication for surgery in IE, as 90% of all deaths result from CHF. It should be noted

TABLE 19.4**ACC/AHA Guidelines: Surgical Intervention for Infective Endocarditis****Class I**

1. Acute native valve IE presenting with valve stenosis or regurgitation that results in heart failure
2. Acute native valve IE presenting with AR or MR with hemodynamic evidence of elevated LVEDP or LAP
3. Native valve IE caused by fungal or other highly resistant organisms
4. Native valve IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions
5. Prosthetic valve IE presenting with heart failure
6. Prosthetic valve IE presenting with dehiscence confirmed by fluoroscopy or echocardiography
7. Prosthetic valve IE presenting with increasing obstruction or worsening regurgitation
8. Prosthetic valve IE presenting with complications such as abscess formation

Class IIa

1. Native valve IE presenting with mobile vegetations > 10 mm with or without emboli
2. Prosthetic valve IE presenting with persistent bacteremia or recurrent emboli despite appropriate antibiotic therapy
3. Prosthetic valve IE presenting with relapsing infection

IE, infective endocarditis; AR, aortic regurgitation; MR, mitral regurgitation; LVEDP, left ventricular end-diastolic pressure; LAP, left atrial pressure

Adapted from the ACC/AHA 2006 Guidelines for the Management of Patients with Valvular Heart Disease. JACC 2006.

that the benefit of surgery persists even in the presence of comorbidities, such as acute renal failure, and surgery should not be delayed in the setting of life-threatening heart failure or cardiogenic shock if the patient is likely to recover after surgery.

3. PVE usually requires a combined medical/surgical approach.
4. **Patients with CNS infarcts or bleeds.** Special attention must be paid to the presurgical candidate who may have had a CNS infarct or bleed, since large doses of heparin are required for cardiopulmonary bypass. Several studies report a significant risk of postoperative neurologic deterioration or even death in patients with recent CNS complications of IE. The best management in the scenario of hemodynamic instability and new-onset embolic stroke has not been addressed in randomized clinical studies. When possible, cardiac surgery is delayed for at least 4 days, ideally 10 days postinfarction in those with a CNS embolic infarct, and for 21 days following an intracranial hemorrhage. However, some patients may need early surgery despite a recent stroke if they are at high risk for recurrent emboli. **If a mycotic aneurysm is found, the timing of surgery should be reconsidered, and any prosthesis that requires postoperative anticoagulation should be avoided.** A ruptured mycotic aneurysm should be resected, clipped, or embolized **before** cardiac operation.
5. Metastatic infection, usually attributed to *S. aureus*, should be drained if accessible.
6. The optimal duration of **antibiotic therapy after surgery** for IE is not known.
 - a. For **native valve IE** caused by an antibiotic-resistant organism with subsequent negative cultures, preoperative plus postoperative antibiotic therapy should consist of a full course of recommended treatment.
 - b. For patients with **positive intraoperative cultures**, a full course of therapy should be given postoperatively.
 - c. Patients with prosthetic valves who are undergoing surgery for IE should receive a full course of antibiotics postoperatively when organisms are discovered in resected material.
- C. The optimal management of **pacer or defibrillator endocarditis** has been controversial in the literature, especially regarding the necessity for device removal.
 1. The success rate without removal of the entire device is low because typically the entire device is infected. Most studies suggest that the complete explantation of all hardware combined with antibiotic therapy is the optimal management.
 2. The optimal route or duration of antibiotics remains unclear in the literature. Experience suggests that a prolonged course of intravenous antibiotics is needed.
 3. The timing of device reimplantation is another important issue. It is prudent to provide sufficient duration of antibiotic therapy to eradicate bacteremia and to suppress or eradicate endocardial infection prior to reimplantation in order to minimize the risk of reinfection of the new device. Studies have shown that reimplantation is successfully performed at a median of 7 days (5 to 25 days) after explantation.

IX. COMPLICATIONS

- A. Table 19.5 lists the complications of IE.
- B. Valve ring abscess is a noteworthy complication of PVE, seen with mechanical and bioprosthetic valves and also occasionally seen in severe infection of native valves. Infection of the sutures used to secure the sewing ring to the periannular tissue may result in dehiscence of the valve. The clinical finding of a new perivalvular leak in a patient with PVE is worrisome. Risk factors for abscess formation include persistent fever, CHF, a history of intravenous drug use, infection with a virulent organism, and PVE.

TABLE 19.5 Complications**Cardiac complications**

Congestive heart failure (leading cause of death)
 Abscess (pericardial, aortic annular, or myocardial)
 Conduction abnormalities (due to invasive disease)
 Coronary embolism
 Mycotic aneurysm (often clinically silent)
 Valvular regurgitation (cusp/leaflet flail or perforation)
 Valvular stenosis
 Prosthetic dehiscence
 Septal perforation (ventricular septal defect)

Extracardiac complications

Systemic embolism (stroke, renal infarct, splenic infarct, or ischemic limb)
 Mycotic aneurysm
 Abscess
 Immune complex deposition (glomerulonephritis)

- X. RESPONSE TO THERAPY.** Although a reduction in the size of vegetations during antimicrobial therapy suggests therapeutic success, vegetations may persist unchanged despite microbiologic cure. Significant enlargement of a vegetation during treatment indicates possible treatment failure and constitutes a relative indication for surgery.
- A.** Blood cultures should be obtained during therapy for IE to ensure eradication of the organism (see Section **V.A.3**).
 - B.** Defervescence usually follows 3 to 7 days of successful antimicrobial therapy. **Persistent or recurrent fever may represent therapeutic failure, drug fever, a secondary nosocomial infection, or intracardiac or extracardiac abscess formation.** Generally, if fever persists for more than 7 days or if blood cultures are positive beyond the first week of antibiotic therapy, the treatment is considered a failure.
 - C.** Relapses, should they occur, usually manifest clinically within 4 weeks and can be confirmed by blood cultures. With a combined medical and surgical approach, recurrent PVE occurs in 6% to 15% of patients.
 - D.** **The frequency of emboli falls rapidly after 1 to 2 weeks of antibiotic therapy,** and the risk is considered to be greatest in the setting of large vegetations (> 10 mm in diameter) and specific infections (*S. aureus* and *Candida*).
 - E.** Medical management is successful in many patients with IE; however, surgery is required in approximately 25% to 33% of cases.
- XI. PROGNOSIS.** The prognosis depends on **the virulence of the causative organism, the underlying health of the patient, the valvular structures, the duration of the infection, and the presence or absence of CHF.** The overall mortality of IE is around 20% to 30%. Notably, the mortality rates in early PVE (40% to 80%) are much higher than in late PVE (20% to 40%). Five-year survival rates after surgery for PVE have ranged from 54% to 87%. In *S. aureus* IE, mortality has decreased from 50% to 60% to 15% to 30% in recent years. The presence of the factors listed in Table 19.6 should trigger an early and aggressive management plan.

TABLE 19.6 Factors and Complications That Predispose to a Poor Outcome

Congestive heart failure (leading adverse prognostic factor)
Nonstreptococcal disease
Aortic valve involvement
Infection of a prosthetic valve
Older age
Abscess formation
HIV with CD4 count < 200 cells/mm ³
Delayed diagnosis
CNS or coronary embolization
Recurrent infective endocarditis

CNS, central nervous system; HIV, human immunodeficiency virus.

- A. There has been an increasing demand to develop an endocarditis risk score for predicting mortality and surgical outcomes in IE. One barrier to the development of this model is inconsistencies in the prognostic value of individual parameters in the published data. These differences may in part be due to time dependencies of various risk factors. One study evaluated risk factors in a time-dependent manner in order to derive a validated risk score for the prognostic evaluation of IE in patients before and during early hospitalization. Factors that contributed to increased mortality included older age, CHF, lower platelet count, higher creatinine, and severe embolic events, consistent with previous studies. A recent study used the Society of Thoracic Surgery database to develop a surgical mortality risk scoring system. Although several studies have attempted to evaluate the most significant predictors of risk, a standardized risk scoring model has yet to be established.

XII. PROPHYLAXIS. Revised IE prophylaxis guidelines from the AHA concluded that **only those patients at highest risk for adverse outcomes from IE require prophylaxis** prior to certain dental or surgical procedures (Tables 19.7A and 19.7B). This is based on studies suggesting that IE is more likely to occur from everyday activities such as flossing or brushing teeth than from dental procedures, and that an extremely small number of cases of IE might be prevented by antibiotic prophylaxis for dental, gastrointestinal, or genitourinary procedures. It is a standard practice (AHA guidelines) that at-risk individuals be counseled and advised to carry a card with current prophylaxis recommendations. Failure to adhere to this practice may invite litigation. A recent study suggests that an echocardiographic report, stating the endocarditis risk and need for prophylaxis, improves compliance with AHA recommendations.

- A. In deciding the need for antibiotic prophylaxis, two factors must be considered: the risk associated with the specific valvular lesion (Table 19.7A) and the type of procedure to be performed (Table 19.7B). Patients for whom antibiotic prophylaxis for IE is recommended include those with **prosthetic heart valves, prior IE, postcardiac transplantation valvulopathy, and certain patients with congenital heart disease** (Table 19.7A). Routine IE prophylaxis is no longer recommended in most cardiac conditions, including mitral valve prolapse, rheumatic heart disease, bicuspid aortic valve, calcific aortic stenosis, atrial septal defect, and ventricular septal defect.

TABLE 19.7A Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Infective Endocarditis

Prophylaxis for endocarditis recommended

Prosthetic heart valves

Previous infective endocarditis

CHD

Unrepaired cyanotic CHD (including palliative shunts or conduits)

Repaired CHD with residual defect at, or adjacent to, the site of repair

During the first 6 mo after repair of congenital heart defects using prosthetic material or device

Cardiac transplantation recipients who develop cardiac valvulopathy

CHD, congenital heart disease.

Adapted from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;115:1–19.

TABLE 19.7B Recommendations for Prophylaxis in Dental or Surgical Procedures

Prophylaxis recommended only in patients at highest risk of adverse outcome from infective endocarditis (Table 19.7A)

Oropharyngeal procedures

Dental procedures that involve manipulation of gingival tissue, the periapical region of teeth, or perforation of the oral mucosa

Tonsillectomy and/or adenoidectomy

Respiratory procedures

Invasive procedures involving incision

Miscellaneous

Procedures on infected skin or musculoskeletal tissue

Adapted from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;115:1–19.

- B. Endocarditis prophylaxis following **dental or oral procedures** is directed primarily against viridans *Streptococcus*; following **genitourinary and gastrointestinal surgery** it is directed primarily against *Enterococcus* organisms.
- C. **Routine antibiotic prophylaxis solely to prevent IE is no longer advised prior to gastrointestinal or genitourinary procedures.** This is based upon an increasing frequency of antimicrobial-resistant strains of enterococci and a lack of evidence conclusively linking these procedures to IE.
- D. Available evidence supports a shift in emphasis away from dental procedures and antibiotic prophylaxis toward a greater **emphasis on maintaining good oral hygiene** and improved access to dental care in patients at risk for IE.

TABLE 19.7C Prophylactic Regimens

Clinical situation	Antibiotic	Dose
Standard prophylaxis	Amoxicillin	2 g PO 1 h before procedure
Unable to take oral medications	Ampicillin	2 g IV or IM within 30 min before procedure
	or Cefazolin or ceftriaxone	1 g IV or IM within 30 min before procedure
Penicillin allergy	Clindamycin	600 mg PO 1 h before procedure
	or Cephalexin	2 g PO 1 h before procedure
	or Azithromycin or clarithromycin	500 mg 1 h before procedure

IM, intramuscular; IV, intravenous; PO, per oral.

Adapted from Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation*. 2007;115:1–19.

- E. Prophylaxis against viridans *Streptococcus* is advised in patients at highest risk of IE who undergo **invasive procedures of the respiratory tract** that involve incision or biopsy (i.e., tonsillectomy or adenoidectomy). Routine endocarditis prophylaxis prior to **vaginal delivery** or hysterectomy is not recommended.
- F. Incision and drainage or other procedures involving infected tissue may result in bacteremia. For nonoral soft-tissue infections, an antistaphylococcal penicillin or first-generation cephalosporin is an appropriate choice of prophylaxis.
- G. Prophylaxis regimens are listed in Table 19.7C. **Cardiac surgical patients** who undergo placement of prosthetic heart valves or other prosthetic material should receive antibiotic prophylaxis, primarily directed against *S. aureus*. A first-generation cephalosporin is commonly used, but the choice of antibiotic should be influenced by the antibiotic susceptibility pattern at each hospital. Prophylaxis should be started immediately before the procedure, repeated during prolonged procedures, and continued for no more than 48 hours. **A careful preoperative dental evaluation** is recommended so that, whenever possible, required dental treatment can be completed before cardiac valve surgery.
- H. **Patients after cardiac transplantation** are at moderate risk for endocarditis because of continuous immunosuppression and the tendency for acquired valvular dysfunction (tricuspid regurgitation from endomyocardial biopsy or rejection).
- I. Pneumococcal vaccination is recommended for all patients with prosthetic heart valves.

XIII. CONTROVERSIES

A. Therapy

1. Short courses of antibiotics (2 weeks) have shown some efficacy in the injection drug user population, as have oral antibiotics in the same population. However, intravenous antibiotics are indicated until conclusive data concerning attentive regimens are available. At least 5 to 7 days of inpatient therapy is advocated before considering outpatient treatment.
2. Correct timing of surgery is often the most difficult and critical decision in the management of IE. It is important to balance the need for medical stabilization

with timely surgery. Kiefer et al. (1) conducted a large multicenter randomized trial of over 4,000 patients with IE and heart failure and showed that surgical intervention during initial hospitalization was associated with decreased in-hospital and 1-year mortality rates. In patients with large mitral or aortic valve vegetations (> 10 mm), early surgery has been found to be associated with decreased mortality and embolic events when compared with conventional medical therapy (3% vs. 23%) in the recently published Early Surgery Versus Conventional Treatment in Infective Endocarditis (EASE) trial. In this trial, patients who had surgery within 48 hours had a decreased rate of all-cause death.

3. Valve repair is a reasonable option for mitral, tricuspid, and, less often, aortic IE in which the infection has been controlled. The choice among mechanical, bioprosthetic, and biologic devices may be made according to the usual criteria. However, in the setting of aortic prosthetic endocarditis, a homograft or an autograft is less likely to become infected than either a xenograft or a mechanical valve and is considered the optimal valve substitute.

ACKNOWLEDGMENTS: *The authors thank Drs. Mateen Akhtar, Xiao-Fang Xu, and Mark Murphy for their contributions to earlier editions of this chapter.*

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CHAPTER

20

Chetan Vagesh Hampole

Rheumatic Fever

- I. **INTRODUCTION.** Rheumatic fever (RF) is a systemic autoimmune disorder related to prior streptococcal infection and is the leading cause of heart disease in those under the age of 40 years living in developing nations.
 - A. The incidence of RF and prevalence of rheumatic heart disease **vary substantially among countries**. In many developing countries, the incidence of acute RF approaches or exceeds 200 per 100,000, whereas in the United States, it is estimated to be less than 1 per 100,000. Since the first half of this century, there has been a

gradual decline in the incidence of RF in the United States, Japan, and most European countries. This is due to improved public health and living conditions, the development of modern antibiotics, as well as a shift in the endemic strains of group A streptococcus (GAS). Localized outbreaks of RF have occurred in the United States as recently as the mid-1980s.

- B. RF is more common among populations at high risk for streptococcal pharyngitis, such as military recruits, those in close contact with school-aged children, and persons of low socioeconomic status. It most commonly occurs between the ages of 5 and 18 years. RF affects both sexes equally, except for Sydenham's chorea, which is more prevalent in females after puberty.

II. CLINICAL PRESENTATION. The clinical manifestations of RF **develop 3 weeks after a GAS tonsillopharyngitis**. It is important to note that one-third of patients with RF do not remember having had a sore throat. Patients with RF present initially with a sudden onset of constitutional symptoms, including fever (101°C to 104°C), malaise, weight loss, and pallor. An exudative and proliferative inflammatory process involving collagen fibrils characterizes the acute phase of RF. **Multiple organ systems**, such as the dermis, central nervous system, synovium, and heart, may be involved. In addition, manifestations may include serositis and involvement of the lungs, kidneys, and central nervous system.

A. Diagnostic criteria

1. The **Jones criteria** are designed to aid in the diagnosis of the first episode of RF. It can be diagnosed when a **previous upper airway infection with GAS is detected in conjunction either with two major manifestations or with one major and two minor manifestations**. Major manifestations include arthritis, carditis, chorea, erythema marginatum, and subcutaneous nodules. Minor manifestations include fever, arthralgias, high C-reactive protein (CRP) level or high erythrocyte sedimentation rate (ESR), and a prolonged PR interval on electrocardiogram (ECG) (Table 20.1).
2. In some circumstances, the **diagnosis of RF can be made without strict adherence to Jones criteria**, as in cases of indolent or recurrent carditis or isolated cases of chorea when other causes have been excluded.

B. Major manifestations (Table 20.1)

1. **Carditis.** This is the most serious and is often regarded as the most specific manifestation of RF, affecting 41% to 83% of patients. It may manifest

TABLE 20.1 **Diagnosis of Rheumatic Fever^a**

GAS infection	Major Jones criteria	Minor Jones criteria
Culture	Carditis	Fever
ASO titers	Arthritis	Arthralgia
Anti-DNase B	Sydenham's chorea	High ESR or CRP
Other antistreptococcal antibodies	Subcutaneous nodules	Prolonged PR
Streptococcal antigens	Erythema marginatum	

ASO, antistreptolysin O; anti-DNase, antideoxyribonuclease B; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GAS, group A streptococcus.

^aThe diagnosis of rheumatic fever requires confirmation of a previous **GAS infection** with at least one of the methods listed above together with either **two major criteria or one major criterion and two minor criteria**.

as pancarditis affecting the endocardium, myocardium, and pericardium simultaneously.

- a. Cardiac involvement ranges from an asymptomatic presentation to progressive congestive heart failure and death.
 - b. The most typical manifestations include **increased heart rate, rhythm disturbances, new murmurs or pericardial friction rub, cardiomegaly, and heart failure**.
 - c. Heart failure is rare in the acute phase; if present, it is usually the result of myocarditis.
 - d. The most characteristic component of rheumatic carditis is a valvulitis (endocarditis) involving the mitral and aortic valves.
 - (1) Mitral insufficiency is the hallmark of rheumatic carditis. Aortic insufficiency is less common and is almost always associated with mitral insufficiency. As a rule of thumb, patients under the age of 30 years tend to present with isolated mitral regurgitation, whereas patients develop mitral stenosis during the third decade, with mixed mitral valve disease predominating thereafter.
 - (2) Acute mitral valve regurgitation produces an apical systolic murmur that may be accompanied by a mid-diastolic Carey Coombs murmur of relative mitral stenosis (a high-pitched early diastolic murmur that varies from day to day). Right-sided valves are rarely involved.
 - (3) Those valvular lesions that are diagnosed by echocardiogram but are clinically silent usually heal without scarring and have a good prognosis. Controversy exists whether echocardiographic findings of mitral regurgitation or aortic insufficiency constitute subclinical rheumatic carditis sufficient to meet the Jones criteria.
 - e. Pericarditis may cause chest pain, friction rubs, and distant heart sounds but is often clinically silent.
2. **Arthritis.** This is the **most common manifestation of RF but is the least specific**. It occurs in 80% of patients and is described as **painful, asymmetric, migratory, and transient. It involves large joints**, such as the knees, ankles, elbows, wrists, and shoulders. It is **more common in older patients and improves markedly with the use of salicylates** within 48 hours of treatment. Monoarthritis, oligoarthritis, and involvement of small joints of the extremities are less common. However, arthritis of the first metatarsophalangeal joint, enthesopathy, and axial involvement, especially of the cervical spine, have also been reported. **Arthritis of RF is benign and self-limiting** (lasting 2 to 3 weeks) and does not result in permanent sequelae. Inflammatory changes without signs of infection are seen in the joint fluid.
3. **Sydenham's chorea.** Also known as Saint Vitus' dance or chorea minor, this **extrapyramidal disorder is characterized by purposeless and involuntary movements** of face and limbs, muscular hypotonia, and emotional lability.
- a. Initial manifestations include difficulty in writing, talking, or walking. Handwriting may deteriorate; speech may change to an explosive and halting tone; and the patient may become uncoordinated and easily frustrated.
 - b. Symptoms tend to be more evident when the patient is under stress or awake and usually disappear during sleep.
 - c. Sydenham's chorea is a **delayed manifestation of RF**, usually appearing 3 months or more after an upper airway infection; it is often the sole manifestation of acute RF. Chorea has been reported in up to 30% of the patients. Most cases tend to follow a benign course, with complete resolution of symptoms in 2 to 3 months, although cases in which symptoms persisted for > 2 years have been reported.

- d. It is important to **differentiate the symptoms of Sydenham's chorea from tics, athetosis, conversion reactions, hyperkinesia, and behavioral abnormalities.**
4. **Subcutaneous nodules.** These usually measure 0.5 to 2 cm and are **firm, painless, and freely mobile nodules that can be isolated or found in clusters** over the **extensor surfaces** of joints (knees, elbows, and wrists), bony prominences, tendons, dorsum of foot, occipital region, and cervical processes. They are seen in up to 20% of patients with RF and last for a few days. The skin overlying the nodules is freely mobile and shows no signs of discoloration or inflammation.
5. **Erythema marginatum.** This is an **evanescent erythematous macular rash** with a pale center of irregular shape. It is **usually nonpruritic and tends to disappear after a few days.** It is highly specific, occurring in < 5% of patients, and is obvious only in fair-skinned individuals. The lesions vary in size and affect mainly the trunk, abdomen, and inner aspect of arms and thighs, but not the face. The rash may be induced by application of heat. Its presence is **suggestive of coexisting carditis.**
- C. **Minor manifestations.** Fever and arthralgias are common, but nonspecific findings of RF that can be used to support the diagnosis of RF when only a single major manifestation is present (Table 20.1).
 1. Fever is encountered during the acute phase of the disease and does not follow a specific pattern.
 2. Arthralgia is defined as pain in one or more large joints without objective findings of inflammation on physical examination.
 3. Other clinical manifestations of RF include **abdominal pain, epistaxis, acute glomerulonephritis, rheumatic pneumonitis, hematuria, and encephalitis.** These are not included as diagnostic criteria for the diagnosis of RF.

III. ETIOLOGY AND PATHOPHYSIOLOGY

- A. The association between tonsillopharyngitis–scarlet fever epidemics and acute RF in the 1930s, the findings of high levels of antistreptolysin O (ASO) in sera of patients with RF, and the confirmation of antibiotics as an efficient mode of prophylaxis of RF provide **strong evidence that GAS is the agent causing initial and recurrent attacks of RF.**
 1. Acute RF might not be caused directly by the bacteria but rather through an immunologic mechanism. Specifically, it appears that patients who develop RF demonstrate a hyperimmune response to GAS, and the level of the immune response correlates with the severity of the RF manifestations. Supporting evidence includes onset approximately 3 weeks following an upper respiratory tract infection, rarity before the age of 5 years when the immune system is still immature, and cross-reactivity between streptococcal cellular antigens and proteins present in human connective tissue.
 - a. The most important antigenic structures (M, T, and R proteins) are localized in the external layer of the bacterial cell wall.
 - b. The M protein not only is responsible for type-specific immunity but also has a powerful antiphagocytic action and is classically regarded as a marker of streptococcal rheumatogenic potential. Patients with acute RF possess high levels of antibodies targeted against this protein. Specific M serotypes of GAS have long been recognized as strong stimulators of a robust immune response and are associated with an increased risk of developing RF. Those M serotypes associated with impetigo or pyoderma may cause glomerulonephritis but are not associated with RF.
 2. In epidemics of streptococcal pharyngitis, it is estimated that approximately **3% of untreated individuals will go on to develop RF.** However, recurrence of

RF is seen in about 50% of patients with a history of RF. For endemic GAS pharyngeal infections, the incidence of RF is much less common.

- B.** Numerous epidemiologic studies favor a **familial and even genetic predisposition**. A monoclonal antibody to B-cell alloantigen (D8/17) is almost universally detected in patients with RF, whereas this antibody is present in < 14% of the general population. In addition, susceptibility to RF has also been linked with D-related human leukocyte antigen 1, 2, 3, and 4 haplotypes. These genetic markers may be useful in the future to identify individuals susceptible to acute RF.

IV. LABORATORY EXAMINATION AND DIAGNOSTIC TESTING. RF is a clinical diagnosis because there is no single laboratory study that is diagnostic of RF.

- A.** Supporting evidence of antecedent GAS infection can be obtained through cultures, antigen test, or serum antistreptococcal antibody test.
1. Although no consensus exists regarding which tests to order at what time, commonly ASO titers and cultures are initially obtained when RF is suspected. Other tests as detailed in the subsequent text are useful only under certain conditions.
 2. A negative throat culture is usually sufficient to withhold antibiotic treatment in most cases, especially if clinical suspicion of RF is low.
 3. Elevated or rising ASO titers provide solid evidence for recent GAS infection. **A greater than twofold rise in ASO titers compared with convalescent titers is diagnostic.**
 4. The probability of detecting a previous GAS infection can be increased by obtaining repeated ASO tests or by looking for antibodies to other streptococcal antigens, such as **antideoxyribonuclease B**.
 5. A slide agglutination test is commercially available, which measures antibodies to several streptococcal antigens. Although this test is simple to perform, it is **not well standardized and is not very reproducible**. Therefore, it is **not recommended** as a definitive test for prior GAS infection.
- B. Biopsies**
1. Aschoff's nodules, a form of granulomatous inflammation, can be seen in the proliferative stage and are considered pathognomonic for rheumatic carditis. They are encountered in 30% to 40% of biopsies from patients with primary or recurrent episodes of RF. Such nodules are most often found in the interventricular septum, the wall of the left ventricle, or the left atrial appendage.
 2. The histologic findings of endocarditis include edema and cellular infiltration of valvular tissue. Hyaline degeneration of the affected valve results in the formation of verrucae at its edge, preventing the normal leaflet coaptation. If the inflammatory process persists, fibrosis and calcification develop, leading to valvular stenosis.
 3. Endomyocardial biopsy does not help in diagnosing first attacks of rheumatic carditis. It is **useful in distinguishing chronic inactive rheumatic heart disease from acute rheumatic carditis**. As such, it is rarely indicated except in cases where recurrent carditis is suspected but cannot be confirmed otherwise.
- C. Other blood tests**
1. As in any inflammatory process, **leukocytosis, thrombocytosis, or hypochromic or normochromic anemia** may be noted.
 2. The favored tests to measure acute phase response are ESR and CRP. Although these tests are nonspecific, they may be helpful in monitoring the inflammatory activity of the disease. These levels are **almost always elevated during the acute phase of RF in patients with arthritis and polyarthritis and are usually normal in patients with chorea**.
- D. Radiography.** Chest radiography may identify increased cardiac size, increased pulmonary vasculature, or pulmonary edema.

E. Electrocardiography and echocardiography. In patients in whom **carditis is subtle and signs of valvular involvement may be mild or transient, a baseline echocardiogram and ECG** may help provide evidence of carditis.

1. The most common finding in the **ECG** is the presence of **PR prolongation and sinus tachycardia**. Myocarditis may prolong the QT interval. In cases of pericarditis, low-voltage QRS complexes and ST-segment changes in the precordial leads can be observed.
2. Echocardiography is likely to show mitral regurgitation or aortic insufficiency. Calcifications of the leaflets and subvalvular apparatus are present in the chronic, not acute, phase of rheumatic heart disease.

VI. THERAPY. It is generally recommended that **patients with suspected RF be admitted for close observation and workup.**

A. Carditis

1. Secondary prophylaxis with penicillin has been shown to reduce not only streptococcal infections but recurrent attacks of acute RF as well. Patients with mild carditis should receive secondary prophylaxis for 10 years after the most recent attack or at least until the age of 25 years, whichever is longer. More severe valvular damage necessitates lifelong secondary prophylaxis.
2. Congestive heart failure should be managed with standard therapy (Chapters 8 and 9).
3. In patients with significant cardiac involvement, corticosteroids are preferred over salicylates. The recommended dose of corticosteroid is 1 to 2 mg/kg/d (maximum of 60 mg/d). Salicylate or steroid therapy does not affect the course of the disease; therefore, the duration of anti-inflammatory therapy is somewhat arbitrary and is guided by the severity of disease and the response to therapy. Commonly, therapy is needed for 1 month in patients with relatively mild cardiac involvement. Therapy should be continued until there is sufficient clinical and laboratory evidence of disease inactivity.
4. After cessation of anti-inflammatory agents, relapse with mild symptoms may occur. **A gradual reduction in steroid dosing is necessary to avoid relapses.** If **symptoms are mild, they usually subside without specific treatment.** For **severe symptoms, treatment with salicylates** should be tried before restarting corticosteroids. Administering salicylate therapy (75 mg/kg/d) while tapering corticosteroids may reduce the likelihood of a relapse.
5. Corticosteroids, despite relieving symptoms or carditis, do not prevent valvular damage.

VI. PREVENTION. See Table 20.2.

A. Primary prevention. The most important step in the management of RF is the eradication of GAS infection, which prevents chronic and repetitive exposure of antigenic streptococcal components to the host immune system. However, **no treatment can eradicate GAS completely in all patients because of high colonization rates.**

1. Early therapy is advisable because it reduces both morbidity and the period of infectivity. Studies have shown that antimicrobial therapy, even when started 9 days after the onset of acute streptococcal pharyngitis, is still effective in preventing primary attacks of RF.
2. Penicillin is the agent of choice primarily for its narrow spectrum of activity, long-standing proven efficacy, and low cost.
 - a. Best results are achieved with a **single intramuscular dose of penicillin G benzathine**. An intramuscular regimen is preferred in patients unlikely to complete a 10-day course of oral therapy or in patients with personal or

TABLE 20.2 Prevention of Rheumatic Fever

Drug	Dosage	Route	Duration
<i>Primary prevention</i>			
Benzathine (penicillin G)	600,000 U (≤ 27 kg) 1.2 million U (≥ 27 kg)	IM	Once
	<i>or</i>		
Penicillin V (children)	250 mg (2–3 times/d)	Oral	10 d
Penicillin V (adolescents and adults)	500 mg (2–3 times/d)	Oral	10 d
Penicillin-allergic patients			
Erythromycin ethyl succinate	40 mg/kg/d (2–4 times/d up to 1 g/d)	Oral	10 d
Erythromycin estolate	20–40 mg/kg/d (2–4 times/d up to 1 g/d)	Oral	10 d
<i>Secondary prevention</i>			
Benzathine (penicillin G)	1.2 million U	IM	q3-4wk
<i>or</i>			
Penicillin V	250 mg	Oral	bid
<i>or</i>			
Sulfadiazine	0.5 g (≤ 27 kg) 1.0 g (> 27 kg)	Oral	qd
Penicillin- and sulfadiazine-allergic patients			
Erythromycin	250 mg	Oral	bid

bid, twice a day; IM, intramuscular; qd, every day.

Adapted from Dajani AS. Rheumatic fever. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia, PA: WB Saunders; 1997:1769–1775.

family history of RF or rheumatic heart disease. This preparation is painful; **preparations that contain procaine penicillin are less painful.**

- b. In comparison with the intramuscular regimen, the oral regimen has several disadvantages, such as lower compliance due to its longer duration, more complicated dosing schedules, drug interactions, and, more importantly, socioeconomic factors. The oral antibiotic of choice is penicillin V (phenoxymethylpenicillin) (see Table 20.2 for dosage information). A broader spectrum penicillin, such as amoxicillin, offers no microbiologic advantage over penicillin.

3. Patients allergic to penicillin:
 - a. Oral erythromycin can be used. The recommended dosage is erythromycin estolate or erythromycin ethyl succinate for 10 days. The maximum dose of erythromycin is 1 g/d.
 - b. Although uncommon in the United States, **strains resistant to erythromycin** have been found in some areas of the world and have caused treatment failures. The newer **macrolides, such as azithromycin**, have the advantage of a short treatment duration (5 days) and few gastrointestinal side effects. These can be used as second-line therapy for patients 16 years or older with GAS pharyngitis. The recommended dosage is 500 mg as a single dose on the first day followed by 250 mg once daily for 4 days.
 - c. Another alternative regimen for penicillin-allergic patients is a **10-day course with an oral cephalosporin**. A first-generation cephalosporin with a narrower spectrum of action (cefadroxil or cephalexin) is preferable to the broader spectrum antibiotics such as cefaclor, cefuroxime, cefixime, and cefpodoxime. Several reports support the evidence that a 10-day course with oral cephalosporin is superior to a 10-day course with oral penicillin and a 5-day course with selected oral cephalosporins is comparable to a 10-day course with oral penicillin for the eradication of GAS.
 - d. Sulfa-derived antibiotics (**sulfonamides and trimethoprim**) **do not eradicate GAS** in patients with pharyngitis, and **tetracycline should be avoided** because of the high prevalence of resistant strains.
- B. **Secondary prevention.** Prophylaxis for preventing recurrences should **start as soon as RF or rheumatic heart disease is diagnosed**, as recurrences can sometimes be asymptomatic.
 1. Penicillin in doses of 600,000 IU (patient's weight < 27 kg) to 1.2 million IU (patient's weight > 27 kg) every 4 weeks is the recommended regimen in most circumstances. The interval is reduced to 3 weeks for individuals at high risk for developing acute RF or living in endemic areas.
 2. The duration of prophylaxis depends on the individual situation. Table 20.3 provides additional information.
 - a. Prophylaxis for **recurrent RF in patients without cardiac manifestations** should be continued for 5 years after the last RF attack or up to the age of 21 years, whichever is longer.

TABLE 20.3 Duration of Therapy for Secondary Prevention of Rheumatic Fever

Disease state	Duration of therapy
RF + carditis + residual valvular disease	At least 10 y postepisode and at least until the age of 40 y. Lifelong prophylaxis may be required
RF + carditis without valvular disease	10 y or beyond adulthood, whichever is longer
RF without carditis	5 y or until the age of 21 y, whichever is longer

RF, rheumatic fever.

Adapted from Dajani AS. Rheumatic fever. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia, PA: WB Saunders; 1997:1769–1775.

- b. For **patients with RF and carditis but no residual valvular disease**, prophylaxis should extend for a period of 10 years or well into adulthood.
 - c. Indefinite antibiotic prophylaxis is recommended in **patients with valvular heart disease**.
- 3. The success of **oral prophylaxis** depends on the patient's understanding and adherence to the prescribed regimen. Oral agents are **more appropriate for patients at lower risk for rheumatic recurrences**. Some favor switching patients to oral prophylaxis when they have reached late adolescence or young adulthood and have remained free of rheumatic attacks for at least 5 years.
 - a. The preferred oral medication is penicillin V.
 - b. For **patients with true or suspected allergy to penicillin, sulfadiazine** can be used (Table 20.2). **Erythromycin** is an alternative.
 - c. It is important to keep in mind that even with optimal patient adherence, the **risk of recurrence is higher with an oral than with an intramuscular prophylactic regimen**.
- C. **Endocarditis prophylaxis**. Updated guidelines from the American Heart Association published in 2007 recommend against routine prophylaxis for endocarditis in patients with rheumatic valvular disease undergoing dental or other procedures. Antibiotic prophylaxis is recommended only for patients with prosthetic valves, previous endocarditis, and certain forms of congenital heart disease and for heart transplant patients with vasculopathy (see Chapter 19).
- D. **Vaccines targeted against GAS**. Several multivalent vaccines against GAS are currently in clinical trials. The M protein is the most promising target, but vaccine development has been complicated because there are multiple M-protein subtypes that are rheumatogenic. The use of a vaccine may prevent pharyngeal colonization, thereby removing population reservoirs, which allow for endemic disease.

VII. SCREENING

- A. **Screening in endemic areas**. Given the significant burden of rheumatic heart disease, screening children and young adults has proven useful for those in endemic areas.
 - 1. Screening generally involves three components: (1) eliciting a history of acute RF, (2) physical examination, and (3) echocardiography. Two screening approaches have been described in high-risk populations. First, physical examination including auscultation for murmur is followed by echocardiographic confirmation in those found to have a murmur. Alternatively, portable echocardiography is used for all followed by clinical examination of abnormal cases. Because auscultation has been shown to be clinician dependent and crude in detecting valve pathology, many cases of rheumatic heart disease go unidentified, favoring the echocardiographic approach to screening.

ACKNOWLEDGMENTS: *The author thanks Drs. Stephen Gimple, Simone Nader, and Mohammed Nasir Khan for their contributions to earlier editions of this chapter.*

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SECTION

IV

Arrhythmias

EDITOR

Thomas D. Callahan

Tachyarrhythmias

I. INTRODUCTION. Tachyarrhythmias have been classically categorized by their location and mechanism. Tachyarrhythmias can originate from ventricular tissue (ventricular tachycardia) or, alternatively can originate from or involve supraventricular tissue (supraventricular tachycardia). The three mechanisms of tachyarrhythmias include abnormal automaticity, triggered activity, and reentry.

A. Abnormal automaticity. Automaticity refers to the ability of cardiac tissue to spontaneously generate pacemaker activity. There are both normal and abnormal sources of automaticity.

1. An example of **normal** accelerated automaticity is the rapid firing rates of a normal pacemaker focus, such as the sinus node (SN), atrioventricular (AV) node, or Purkinje system due to ischemia, metabolic disturbance, exercise, or pharmacologic manipulation. A clinical example would be accelerated **sinus tachycardia** or **junctional rhythm**.

2. Abnormal automaticity refers to tissues that under normal circumstances do not demonstrate automaticity, but can become automatic in the setting of ischemia, metabolic disturbance, or pharmacologic manipulation. Overall, abnormal automaticity is responsible for < 10% of tachyarrhythmias. These latent or ectopic loci of cells generate automatic, spontaneous impulses that usurp control of the cardiac rhythm. These usually have a warm-up and cool-down period and cannot be induced by programmed electrical stimulation. A clinical example would be **accelerated idioventricular** rhythm (see Section IV.C.1) or **multifocal atrial tachycardia** (see Section II.F).

B. Triggered activity refers to pacemaker activity that is dependent on afterdepolarizations from a prior impulse or series of impulses. Afterdepolarizations are oscillations in the membrane potential. If these reach the critical threshold for depolarization of the surrounding cardiac tissue, they may trigger an action potential, thereby precipitating further afterdepolarizations and perpetuating the pacemaker activity. The two categories of afterdepolarizations are early and delayed.

1. Early afterdepolarizations (EADs) occur before repolarization of the cardiac tissue is completed (during phase 3 of the action potential) and may be the mechanism responsible for the ventricular arrhythmias of the **long QT syndromes (LQTSs)**, as well as **torsade de pointes** ("twisting of the points") produced by class I and class III antiarrhythmics, sympathetic discharge, and hypoxia. Antibiotics such as macrolides, certain azole antifungal agents, some psychotropic medications such as haloperidol, and several nonsedating antihistamines have been shown to produce EADs. Rapid heart rates and the administration of magnesium have been shown to suppress EADs.

2. Delayed afterdepolarizations (DADs) occur after the repolarization of the surrounding tissue is complete (during phase 4 of the action potential) and are thought to be the mechanism of triggered atrial tachycardia, arrhythmias of **digitalis toxicity**, and rare ventricular tachycardias (VTs) responsive to calcium channel blockers. These have been demonstrated in various cardiac issues, including

parts of the conducting system, myocardial cells, and valve tissues. Increases in intracellular calcium are associated with DADs, such as those caused by digitalis preparations or excessive sympathetic stimulation. Drugs that block the influx of calcium (such as calcium channel blockers and β -blockers) and drugs that decrease the sodium current (such as lidocaine and phenytoin) suppress the occurrence of DADs, whereas rapid heart rates augment DADs.

C. Reentry. **Reentry is the most common cause of tachyarrhythmias.** In order for reentry to occur, **three conditions** must be met:

1. Two functionally distinct conducting pathways must connect to form a circuit.
2. Unidirectional conduction block occurs in one of the pathways due to differences in refractory periods (block occurs in pathway with the longer refractory period).
3. Slow conduction occurs down the unblocked pathway (which has the shorter refractory period), allowing the blocked pathway time to recover excitability and sustain the arrhythmia.

Reentrant circuits can occur in the sinus node, the atrium, the AV node, between the atrium and ventricle via bypass tracts, and within the ventricle itself. The typical substrate for malignant reentry in the ventricle is **scar or ischemia**, which can produce regions in the heart that **depolarize and repolarize heterogeneously**. Therefore, the impulse can spread to an area that has already repolarized after being previously depolarized. This can set up a circular movement of the impulse resulting in sustained tachyarrhythmias such as VT. Reentry can typically be induced by premature electrical stimulation during electrophysiologic testing.

Elucidation of the mechanisms of tachyarrhythmias has led to the development of catheter-based treatment strategies and more advanced medical therapy.

II. SUPRAVENTRICULAR TACHYARRHYTHMIAS

A. Sinus tachycardia

1. **Clinical presentation.** Sinus tachycardia manifests as sinus rhythm with a rate above 100 beats/min. Although the rate may be as high as 200 beats/min in younger individuals, it is generally **150 beats/min or less in older individuals**.
2. **Pathophysiology**
 - a. The SN is an epicardial structure that is located laterally near the junction between the superior vena cava and the right atrium. Under normal circumstances, the rate of SN discharge is governed by sympathetic and vagal stimulation.
 - b. Sinus tachycardia generally reflects **an underlying process, metabolic state, or effect of medication**. Fever, hypovolemia, shock, congestive heart failure (CHF), anxiety, pulmonary disease including pulmonary embolism, anemia, thyrotoxicosis, caffeine, nicotine, atropine, catecholamines, or withdrawal from alcohol or drugs (both therapeutic and illicit) can cause sinus tachycardia.
 - c. Sinus tachycardia can be appropriate, where it represents a normal physiologic response, **or inappropriate**, as in defects in vagal or sympathetic tone or an intrinsic problem with the SN itself.
 - d. The **clinical consequences of sinus tachycardia vary** based on the presence or absence of underlying heart disease. Patients with significant coronary artery disease (CAD), left ventricular (LV) dysfunction, or valve disease may not tolerate sinus tachycardia. Patients with inappropriate sinus tachycardia may experience significant symptoms such as palpitations, dyspnea, and/or chest pain.
3. **Diagnostic testing.** Electrocardiography is the primary diagnostic test. The main differential is between sinus tachycardia, sinus node reentry tachycardia (SNRT) (see Section **II.B**), and inappropriate sinus tachycardia. Inappropriate sinus tachycardia is characterized by the following features: (a) **heart rate > 100 beats/min**, (b) **P-wave axis and morphology during tachycardia similar or identical to that during sinus rhythm**, (c) **exclusion of secondary causes**

- of sinus tachycardia, (d) exclusion of atrial tachycardias, and (e) symptoms clearly documented to be related to resting or easily provoked sinus tachycardia.
4. Therapy is generally directed at the elimination of the underlying cause whenever possible.
 - a. If withdrawal from a therapeutic medication is suspected, then reinstitution or slow tapering of this medication can be attempted, if clinically appropriate.
 - b. In the case of **inappropriate sinus tachycardia, β -blockers and calcium channel blockers** may be necessary to control the heart rate.
 - c. In **medically refractory cases, catheter ablation for sinoatrial nodal modification** may have to be considered.
- B. SNRT** accounts for 5% to 10% of all supraventricular tachyarrhythmias.
1. **Clinical presentation.** SNRT is most frequently seen in patients with structural heart disease or CAD, especially in inferior myocardial infarctions (MIs). The rate varies from 80 to 200 beats/min. SNRT's characteristic abrupt onset and termination (paroxysmal nature) along with its ability to be induced and terminated by pacing imply that the underlying mechanism is reentry and distinguish it from sinus tachycardia and inappropriate sinus tachycardia.
 2. **Pathophysiology.** Reentry occurs within or adjacent to the SN and then conducts via the normal conduction pathway to the rest of the heart. The morphology of the P wave is identical to the underlying sinus morphology. Block at the AV node may occur, but it does not slow the tachycardia. In fact, a Wenckebach-type block often occurs with this rhythm. The development of a bundle branch block does not affect the cycle length or the PR interval.
 3. **Therapy.** Vagal maneuvers or adenosine may successfully terminate this arrhythmia. **Rapid atrial pacing** can be used to induce and terminate this tachycardia. Various agents such as β -blockers, calcium channel blockers, and digoxin may help prevent recurrences. SN ablation or modification is rarely necessary.
- C. Atrial fibrillation (AF)** is the most common sustained arrhythmia, occurring in up to 1% of the general population. The prevalence of AF increases with age, affecting up to 10% of the population older than 80 years (see Chapter 24).
- D. Atrial flutter.** Atrial flutter is the **second most common of the atrial tachyarrhythmias**. Its reported incidence varies from 0.4% to 1.2% in hospital reports of electrocardiogram (ECG). The **clinical significance of atrial flutter is generally due to its association with AF** (with all of the attendant risks of AF) and/or its association with rapid rates of ventricular response.
1. **Clinical presentation.** The clinical presentation may vary widely depending on the presence of underlying heart disease, the ventricular rate, and the overall condition of the patient. It is **occasionally reported to persist for days** and, less commonly, for weeks or longer. Careful examination of the jugular venous pulse may reveal **frequent, regular a waves** that correspond to the atrial flutter rate. Like AF, it is **commonly seen after open heart surgery, as well as with other conditions commonly associated with AF**, such as pulmonary disease, thyrotoxicosis, atrial enlargement due to any cause including mitral/tricuspid valve disease, and SN dysfunction.
 2. **Pathophysiology.** "Typical" atrial flutter is the **result of a macroreentrant circuit in the right atrium**. Atypical atrial flutter generally involves other macroreentrant circuits around scar tissue or surgical incisions.
 - a. **In a typical atrial flutter, the reentrant circuit most commonly travels in a counterclockwise rotation** down the right atrial anterolateral free wall across the cavotricuspid isthmus (area of slow conduction) and up the interatrial septum. Clockwise rotation of this circuit may also be seen.

- b. Atrial flutter has been classified into type I and type II based on the following characteristics:
 - (1) Type I atrial flutter can be terminated with rapid atrial pacing and typically has an atrial rate in the range of 240 to 340 beats/min in the absence of drug therapy.
 - (2) Type II atrial flutter cannot be terminated with rapid atrial pacing and typically has an atrial rate in the range of 340 to 440 beats/min in the absence of drug therapy.
 - (3) Types I and II are not synonymous with typical and atypical atrial flutters. Type I atrial flutter can include typical and atypical atrial flutters. Type II atrial flutter is less well characterized than type I with respect to etiology and therapy; therefore, **we refer to type I atrial flutter throughout this discussion.**
3. **Laboratory examination**
- a. The **diagnosis can be difficult when the AV conduction is 2:1**, as the flutter waves may be superimposed on the QRS complex and/or the T waves. When the diagnosis is uncertain, one should **consider maneuvers or medications to slow the ventricular response**, thus revealing the atrial flutter complexes.
 - (1) Vagal maneuvers include carotid sinus massage and Valsalva maneuver. **Caution must be exercised** when attempting carotid sinus massage **in patients with known or suspected carotid disease** or vagal maneuvers **in patients with CAD who are at risk for ischemia.**
 - (2) Adenosine can be administered, 6 mg rapid intravenous push, followed by 12 mg if there is no response (a second 12-mg dose can be given if there is no response). The half-life of this medication is very short, approximately 9 seconds. This causes transient (lasting seconds), complete AV block. Alternative agents include the intravenous calcium channel blocking agents **verapamil and diltiazem** and the intravenous β -blockers **esmolol and metoprolol**. Patients should be connected to a transcutaneous pacing device during the administration of this medication for reasons of safety.
 - (3) The clinician can place and record from a **transesophageal electrode** or record from a **temporary atrial epicardial pacing wire** (placed at open heart surgery). This results in an ECG with clearer atrial complexes and thus simplifies diagnosis. This strategy also allows a method of delivering rapid atrial pacing in an attempt to terminate the atrial flutter.
 - b. On the surface ECG, typical counterclockwise atrial flutter shows the **classic negatively directed “sawtooth” waveform** in the inferior leads (II, III, and aVF) (Fig. 21.1). Conversely, the atrial depolarizations are positive in these leads in clockwise atrial flutter (Fig. 21.2).
 - c. The **atrial rate** in the absence of drug therapy is **240 to 340 beats/min**.
 - d. The **QRS complex should be the same as that seen during sinus rhythm** although aberrant conduction may occur, and the QRS may be slightly distorted by the atrial flutter waves.
 - e. The **ventricular response** can be irregularly irregular, due to varying degrees of block (2:1, 4:1, and so on), but is more **typically regular as a fixed ratio of the flutter rate.**
4. **Therapy**
- a. Medical therapy differs very little from that for AF (see Chapter 24).
 - (1) Control of the ventricular response rate with a β -blocker, a calcium channel blocker, or digoxin is critical prior to initiating therapy with agents such as the class IA or IC agents. The class IA or IC agents either enhance AV nodal conduction through their vagolytic effects, thereby enabling 1:1 (AV) conduction, or slow the atrial rate to a point where 1:1 conduction is facilitated.

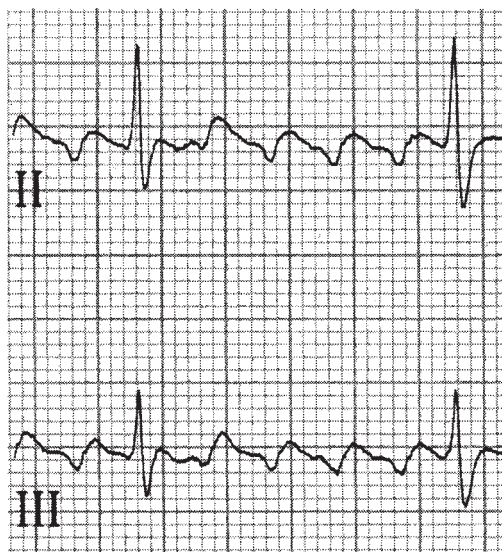


FIGURE 21.1 “Typical” atrial flutter, leads II and III.

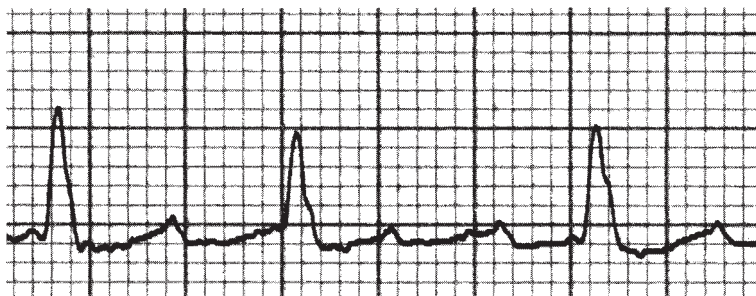


FIGURE 21.2 “Atypical” atrial flutter, lead II.

- (2) The conversion from atrial flutter to AF after cardioversion is substantially reduced by the administration of antiarrhythmic drugs prior to direct current cardioversion (DCC), thereby increasing the chance of converting to sinus rhythm.
- (3) **Anticoagulation.** There are no prospective data looking at the incidence of thromboembolic events with atrial flutter. However, retrospective data suggest an increased incidence of thromboembolic events. Recent ACCP (2004) and ACC/AHA/ESC (2006) guidelines recommend managing anticoagulation in atrial flutter in a manner similar to that for AF, including cardioversions. Optimal management is unclear and often needs to be individualized with the patients' profile for thromboembolic risk dictating the type and duration of therapy. We treat atrial flutter in a manner similar to that used for AF with regard to anticoagulation.

b. Direct current cardioversion

- (1) DCC is the preferred and most effective therapy for most patients. The procedure is detailed in Chapter 59. A starting energy as low as 25 to 50 J is often effective. Because DCC may result in conversion from atrial flutter to AF, a second shock is sometimes necessary to convert AF to sinus rhythm.
- (2) Rapid atrial pacing should be considered as the **first line of therapy for all patients who have epicardial atrial pacing wires in place after open heart surgery**. It may be considered via a transesophageal pacing lead or via a transvenously placed pacing lead in patients for whom DCC fails or who are not candidates for DCC. **Before attempting to rapidly pace the atria, it must be confirmed that ventricular capture is not inadvertently occurring** by first pacing at a relatively slow rate while observing for such a phenomenon. Once this is confirmed, the atrium is paced at a rate of 10 to 20 beats/min faster than the underlying atrial flutter rate. Once atrial capture is attained, the rate is increased steadily until the hallmark negative-sawtooth waveform converts to a positive waveform. The pacing is then either halted abruptly or slowed rapidly to an acceptable atrial pacing rate. In cases that require extremely rapid rates of pacing (> 400 beats/min) or high amplitudes of pacing stimulus strength (> 20 mA), there is an increased tendency for the atrial flutter to convert to AF. **When pacing via a transesophageal lead, a higher stimulus strength (up to 30 mA) may be necessary. Because this type of pacing can be quite painful**, a sufficient energy to convert the atrial flutter should be used initially to minimize the conversion attempts.
- (3) **Percutaneous therapy**. Radiofrequency ablation (RFA) of the cavotricuspid isthmus is often curative, with an efficacy > 90% for the long-term elimination of atrial flutter. Despite the high success rate of catheter-based therapy, a significant number of patients may subsequently develop AF.

E. Atrial tachycardias. This term encompasses a number of different types of tachycardias that originate in the atria. These tachycardias account for between 10% and 15% of the tachycardias seen in older patients, usually in the setting of structural or ischemic heart disease, chronic obstructive pulmonary disease, electrolyte imbalances, or drug toxicity (particularly digitalis).

1. Clinical presentation. These tachycardias are **infrequently seen in younger, healthy patients without underlying heart disease**. They are **typically paroxysmal**, but if incessant they can lead to a tachycardia-induced cardiomyopathy.

2. Diagnostic testing**a. ECG**

- (1) The **P-wave axis** or morphology is usually different from that of sinus rhythm. One exception is atrial tachycardias originating from the right superior pulmonary vein, which is anatomically close to SN. The axis can be used to predict the origin of the atrial tachycardia.
 - (2) Atrial rhythm is regular, except with automatic atrial tachycardia, which displays a warm-up period (see Section II.E.3.b).
 - (3) A **QRS complex that is generally identical to sinus rhythm** (QRS can be wide if aberrant conduction occurs) follows each P wave.
 - (4) PR interval is within normal limits or prolonged.
 - (5) Nonspecific ST-T-wave changes may be present.
 - (6) When an AV block is present, there is an **isoelectric baseline** between P waves in all leads.
- b.** Electrophysiologic study has become critical in determining the underlying mechanism of these tachycardias, as the clinical differences are subtle and overlapping.

3. **Subclassifications.** The current subclassifications are **based on mechanisms** and include automatic atrial tachycardia, triggered atrial tachycardia, and intra-atrial reentry.
 - a. Intra-atrial reentry is usually a disorder **seen in those with underlying heart disease or history of atrial arrhythmia**, such as AF or atrial flutter. The mechanism is not well understood. The ventricular rate is typically 90 to 120 beats/min due to the frequent occurrence of 2:1 AV block, such that hemodynamic effects are generally minimal. This rhythm can be difficult to distinguish from other supraventricular tachyarrhythmias. One clue is that despite any AV conduction block, the rhythm continues. The ability to terminate with adenosine and β -blockers is variable. **RFA may be effective**, with success rates $> 75\%$. **Antiarrhythmics** (the same drugs as for AF and atrial flutter) **have been disappointing in the prevention of recurrence**.
 - b. Automatic atrial tachycardia appears to be generated by an ectopic atrial focus, which usually arises from regions around the crista terminalis in the right atrium and around the base of the pulmonary veins in the left atrium. The mechanism is not well understood. Automatic atrial tachycardia is **seen more often in younger patients**, displays a **warm-up phenomenon** (the supraventricular tachyarrhythmia accelerates after its initiation), **does not respond to vagal maneuvers, and is more likely to be incessant**. Automatic atrial tachycardia can be induced with treadmill testing or with administration of isoproterenol. Atrial stimulation during electrophysiologic study has no effect on either initiating or terminating this arrhythmia. **Propranolol** has been used successfully to suppress automatic atrial tachycardia. **Catheter ablation is the preferred therapy when the tachycardia is incessant**. Although adenosine may transiently slow automatic atrial tachycardia, it is unlikely to terminate it. Likewise, verapamil has been used without success.
 - c. Triggered atrial tachycardia is the least common of the atrial tachycardias and is virtually never incessant. It is more likely to appear in **older individuals**. It can be induced with rapid atrial pacing and is cycle length–dependent. The mechanism of triggered atrial tachycardia is thought to be due to DADs (see Section **I.A.2**) secondary to digitalis toxicity or sympathetic discharge. Catecholamines may play a role in the initiation of this arrhythmia, and thus exercise testing and isoproterenol may provoke it. Verapamil and adenosine have been shown to terminate triggered atrial tachycardia. β -Blockers have been less effective. **RFA** is preferred when the tachycardia is very symptomatic and not responsive to medication.

F. Multifocal atrial tachycardia

1. **Clinical presentation.** This atrial arrhythmia is uncommon and estimated to occur in 0.37% of hospitalized patients. The atrial rate is generally 100 to 130 beats/min. It occurs most often in elderly, critically ill patients and is frequently **associated with concurrent pulmonary disease, particularly chronic obstructive pulmonary disease**. It may also be seen in CHF and can degenerate into AF.
2. **Pathogenesis and diagnostic tests.** The mechanism appears to be abnormal automaticity or triggered activity arising from distinct atrial sites. The diagnosis requires the following criteria: (1) atrial rate > 100 beats/min, (2) P waves with three or more different morphologies, (3) varying P-P, P-R, and R-R intervals, and (4) the P waves separated by isoelectric intervals. Loss of AV conduction of each P wave is uncommon, making it possible to distinguish multifocal atrial tachycardia from AF.
3. **Therapy is directed at the underlying illness, with little role for antiarrhythmics.** Calcium channel blockers in high doses may be useful, or amiodarone when antiarrhythmic therapy is deemed necessary. Maintenance of electrolyte balance, particularly potassium and magnesium, may suppress the occurrence of multifocal atrial tachycardia.

G. Atrioventricular nodal reentrant tachycardia (AVNRT)

1. **Clinical presentation.** AVNRT usually has a narrow QRS complex with a ventricular rate typically in the range of 150 to 250 beats/min, although faster rates are infrequently observed. AVNRT is generally seen in patients without underlying heart disease. Palpitations and dyspnea are common presenting complaints. Angina, CHF, and rarely shock may be seen in those with a history of underlying heart disease. Syncope may occur due to rapid ventricular rates or due to asystole or bradycardia seen occasionally when this tachycardia terminates.
2. **Pathophysiology.** The mechanism in AVNRT appears to be a reentrant circuit composed of separate fast and slow atrial pathways involving the AV node. In 50% to 90% of patients with “typical” AVNRT, the antegrade conduction to the ventricles travels over the slow pathway and the retrograde conduction to the atria occurs over the fast pathway. The initiating event may be either a premature atrial complex (PAC) or a premature ventricular complex (PVC). The PAC blocks the fast pathway antegradely and conducts down the slow pathway, then backs up the fast pathway after it has repolarized. Less commonly, a PVC conducts retrogradely to the atria via the fast pathway and then returns to the ventricles via the slow pathway. In the remaining 5% to 10% of patients, with atypical AVNRT, the antegrade conduction is down the fast pathway and retrograde via the slow pathway. The cycle length is thus dependent on the conduction velocity of the slow pathway, since the fast pathway generally has rapid conduction. Termination of the tachycardia is often the result of a block in the slow pathway. AV dissociation may develop during the tachycardia because the ventricles are not involved in the reentry circuit. This does not affect the rate of tachycardia nor does the development of bundle branch block.
3. **Laboratory features and diagnosis.** P waves are generally hidden within the QRS complex or at the terminal portion of the QRS in typical AVNRT. This may be visible as a small pseudo-R' in lead V₁ or small negative deflections in the inferior leads, as depolarization of the atria occurs simultaneously with ventricular depolarization. The RP segment is generally < 100 milliseconds. AVNRT is often induced abruptly by a PAC and its termination, which also tends to be abrupt, is often followed by a retrograde P wave. The termination may be followed by a brief period of asystole or bradycardia before the SN recovers from its tachycardia-induced suppression. The cycle length may vary, especially at the beginning and at the end of the tachycardia. This variation reflects the variable antegrade AV nodal conduction time. Vagal maneuvers may slow or terminate this tachycardia.
4. **Therapy.** Presently, the success and safety of percutaneous catheter ablation have allowed this approach to be considered equally with medical therapy as first-line therapy for long-term management of AVNRT. The decision about treatment approach should be individualized according to the characteristics of each patient and his or her arrhythmic patterns.
 - a. RFA has the advantage of curing the arrhythmia in the majority of instances and eliminating the need for long-term suppressive therapy with medications. Cure rates with catheter ablation for AVNRT are in excess of 95%.
 - b. **Medical therapy.** Medications that suppress AV nodal conduction such as β -blockers, calcium channel blockers, digoxin, and adenosine all slow or block conduction in the antegrade slow pathway, whereas class IA and class IC antiarrhythmic drugs slow the conduction in the retrograde fast pathway. Adenosine may be considered as first-line drug therapy for acute termination of AVNRT. This medication is available in an intravenous form only and has a very short half-life of about 9 seconds. The use of intravenous or oral β -blockers or calcium channel blockers is an alternative if adenosine is unsuccessful. The onset of action of digoxin limits its usefulness in terminating these arrhythmias, although it may be useful to prevent recurrences. Recurrences may be prevented in patients

with frequent sustained episodes with any of the above-mentioned agents except adenosine. Antiarrhythmic drug therapy is not routinely necessary or desirable for AVNRT, given the high success rates and low complication rates for catheter ablation.

- c. DCC should be considered for patients whose disease is unstable or highly symptomatic. Low energies of 10 to 50 J are usually sufficient to terminate AVNRT.

H. Atrioventricular reentrant tachycardia (AVRT)

1. **Clinical presentation.** Similar to AVNRT, this is another example of an AV nodal-dependent supraventricular tachycardia (SVT). AVRT usually has a narrow QRS with ventricular rates similar to those of AVNRT, although it more often tends to have a ventricular rate > 200 beats/minute. The clinical features are very similar to those of AVNRT but are distinct on an electrophysiologic basis.
2. **Pathophysiology.** The mechanism in AVRT relies on the presence of an accessory pathway as one portion of the circuit and the AV node as the other portion. The atrium and the ventricle on the same side as the accessory pathway are necessary components of the circuit. AVRT may be orthodromic or antidromic. Orthodromic AVRT usually has a narrow complex that uses the AV node as the antegrade limb and the accessory pathway as the retrograde limb of the circuit. Antidromic AVRT has a wide complex that is the opposite of the orthodromic variety, such that the accessory pathway serves as the antegrade limb and the AV node as the retrograde limb of the circuit. AVRT is most often of the orthodromic type. Accessory pathways may be “concealed” (inapparent by ECG) because of having only retrograde (V to A) conduction properties or “manifest” (apparent on ECG as delta waves, i.e., Wolff-Parkinson-White [WPW] pattern). **Unlike AVNRT, the AVRT circuit must involve one of the ventricles; therefore, the development of bundle branch block on the side ipsilateral to the accessory pathway can prolong the ventricular to atrial conduction time and often the cycle length of the tachycardia.** Bundle branch block, particularly left bundle branch block (LBBB), occurs more commonly in AVRT than in AVNRT. AVRT can be distinguished from AVNRT by electrophysiologic study. The presence of AV or ventriculoatrial (VA) block with continuation of the tachycardia should exclude the presence of an accessory AV pathway.
3. **Laboratory features and diagnosis.** The P waves of AVRT are frequently inscribed on the ST segment or T wave, as the atrial depolarization and ventricular depolarization are in series rather than in parallel. The RP segment is generally > 100 milliseconds. Orthodromic AVRT is more common, accounting for about 95% of all AVRTs, whereas antidromic AVRT accounts for only about 5%. Orthodromic AVRT is usually characterized by a narrow QRS complex as opposed to antidromic AVRT, which is characterized by a wide QRS complex.
4. **Therapy.** See the discussion of therapy for WPW syndrome (Section I.4).
- I. **Preexcitation syndromes.** Preexcitation was originally used to describe the premature activation of ventricle in patients with WPW. The term has broadened to include all conditions in which antegrade ventricular activation or retrograde atrial activation occurs partially or totally via an anomalous pathway distinct from the normal cardiac conduction system. The incidence of preexcitation on ECG is approximately 1.5 per 1,000 cases, most of which occur in otherwise healthy subjects without organic heart disease. About 7% to 10% of these patients have associated Ebstein’s anomaly and are thus more likely to have multiple accessory pathways. There is a higher rate of preexcitation in males, with the **prevalence** decreasing with age, although the **frequency** of paroxysmal tachycardia increases with age.
 1. **Clinical presentation.** Approximately 50% to 60% of patients with preexcitation report symptoms such as **palpitations, anxiety, dyspnea, chest pain or tightness, and syncope**. In approximately 25% of the cases, the disease will

become asymptomatic over time. Those patients older than 40 years whose disease has been asymptomatic are likely to remain symptom free. The absence of preexcitation on ECG despite the discovery of accessory pathways in patients with asymptomatic disease likely identifies a group of patients at low risk for developing symptoms.

2. **Pathophysiology.** Patients with preexcitation generally have an accessory pathway(s) that alters the conduction between the atria and the ventricles. These accessory pathways are likely congenital, as relatives of subjects with preexcitation have an increased incidence of preexcitation. AVRT is the most common mechanism associated with preexcitation (80% to 85%), with permanent junctional reciprocating tachycardia, Mahaim fiber tachycardia, and Lown-Ganong-Levine (LGL) syndrome accounting for the remainder.
 - a. **WPW syndrome.** The basic abnormality lies in the existence of an accessory pathway of conducting tissue, outside of the normal conducting system, which connects the atria and the ventricles. This accessory pathway permits the atrial impulse to bypass the normal pathway through the AV node to the ventricles. In the past, these accessory pathways have been referred to as “bundles of Kent.” An impulse from the atria can be conducted down both the accessory pathway and the AV node, arriving at the ventricle at nearly the same time. This results in preexcitation of the ventricle, which is really a fusion beat, as a portion of the ventricle is activated via the accessory pathway (giving rise to the delta wave; Fig. 21.3) and the remainder of the ventricle is activated by the normal activation pathway. If antegrade conduction occurs exclusively via the accessory pathway, the resultant QRS is maximally pre-excited and is a wide complex. These accessory pathways may conduct rapidly, but frequently have longer refractory periods than the AV node. The inciting event for AVRT is frequently a PAC that is blocked in the accessory pathway and that conducts to the ventricles via the AV node, which has recovered more rapidly. The resultant QRS complex in this instance is normal in appearance. After the QRS complex, the accessory pathway has had sufficient time to recover excitability, and the impulse thus conducts retrogradely to the atria. A small but significant percentage (5% to 10%) of patients have multiple accessory pathways.
 - b. Permanent junctional reciprocating tachycardia is a variant of AVRT. It is often an incessant supraventricular tachyarrhythmia with an unusual accessory pathway. Here, the accessory pathway behaves like the AV node in that it displays decremental retrograde conduction properties. Thus, the faster the stimulation of such an accessory pathway, the slower the conduction through the pathway. The accessory pathway is most often located in the posteroseptal region and acts as the retrograde limb of the reentrant circuit. The VA conduction is slowed by the decremental nature of the accessory pathway. Due to the incessant nature of this tachycardia, a tachycardia-induced cardiomyopathy may result.
 - c. **Mahaim fiber tachycardias are another variant of reentrant tachycardia.** The two most common varieties that are recognized are **atriofascicular** and **fasciculoventricular**. In the former, the accessory pathway is located within a few centimeters of the AV node and inserts into the right bundle branch. The reentrant tachycardia conducts antegrade via the accessory pathway, resulting in an LBBB morphology with left-axis deviation. The retrograde circuit is via the AV node. In the second form of Mahaim reentry, the accessory pathway arises in the His-Purkinje fibers and allows bypass of the distal conducting system.
 - d. LGL syndrome is diagnosed by the presence of a short PR interval and a normal QRS complex on the surface ECG. LGL syndrome likely represents one

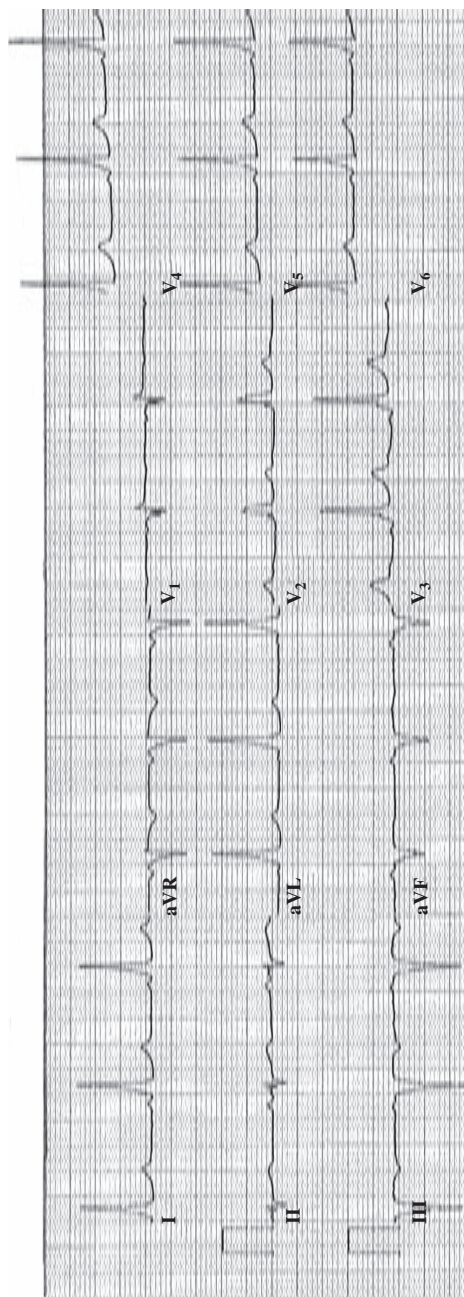


FIGURE 21.3 Wolff-Parkinson-White syndrome, with widespread delta waves seen at the upstroke of the QRS complexes.

end (enhanced) of the normal spectrum of AV nodal conduction properties, but in some cases it is impossible to exclude a distinct perinodal accessory pathway or an abnormality in conduction characteristics of the AV node. It is uncertain if this abnormality in AV conduction is itself associated with arrhythmias.

3. Diagnostic testing

- a. The following electrocardiographic criteria are suggestive of an accessory pathway consistent with a WPW pattern. The WPW syndrome occurs in the setting of the WPW pattern and SVT.
 - (1) The PR interval is short, typically < 120 milliseconds.
 - (2) The QRS complex exceeds 120 milliseconds, with some leads showing the characteristic slurred upstroke known as a delta wave (Fig. 21.3) and a normal terminal QRS portion.
 - (3) The ST-T segment is directed opposite to the major delta and QRS vectors.
- b. The most commonly seen tachycardia in WPW syndrome is characterized by a normal QRS with a regular rate of 150 to 250 beats/min. Onset and termination are abrupt.
- c. **Localization of accessory pathway.** The **surface ECG** may provide information that allows localization of the accessory pathway. The simplest classification is that of type A or type B. **Type A** has a large R wave in lead V_1 . It is due to a left-sided accessory pathway, which permits preexcitation to the posterobasilar segment of the left ventricle. **Type B** has an S or QS in lead V_1 and is due to a right-sided accessory pathway. When present, the morphology of a retrograde P wave can be helpful in predicting the location of the accessory pathway. More elaborate algorithms for localization are available. The **most precise localization method is electrophysiologic study** with ventricular pacing or during orthodromic AVRT (the latter condition is especially helpful as there is VA conduction purely through the accessory pathway, and fusion with VA conduction through the AV node is, therefore, avoided). A positive P wave in lead V_1 during supraventricular tachyarrhythmia suggests a left free wall pathway, whereas a negative P wave suggests a right-sided pathway.
- d. Risk stratification should be considered for patients with WPW pattern or ventricular preexcitation according to ECG findings. The appearance or disappearance of preexcitation on **serial ECGs is of no predictive value**. However, **the intermittent loss or appearance of preexcitation on a beat-to-beat basis is indicative of lower risk**. This may be assessed with ambulatory Holter monitoring during usual activities or with formal exercise stress testing. Such intermittent preexcitation suggests a pathway without the ability for rapid AV conduction and, therefore, lower risk of sudden cardiac death (SCD). However, the reverse is not necessarily true in that most patients with persistent preexcitation may still be at low risk for SCD, but these patients cannot be distinguished from those at risk. As the greatest danger to patients with preexcitation may be the development of AF, **the induction of AF may be most useful in risk stratification**. This can be done via transesophageal pacing; however, electrophysiologic study is the procedure of choice for risk stratification in patients with persistent ventricular preexcitation.

4. Therapy

- a. **Emergency management of acute tachycardia episodes.** A patient **demonstrating hemodynamic instability or extreme symptomatology should be cardioverted rapidly**. Stable patients may be treated medically.
 - (1) **Normal QRS width.** Both types of AVRT (orthodromic and antidromic) are AV node-dependent and thus respond to AV nodal blocking therapies. Although it is reasonable to use vagal maneuvers and AV nodal

blocking medications acutely in patients presenting with a narrow QRS (immediate synchronized DCC should be available should the rhythm degenerate), it is not safe in patients when they present with a wide QRS. Atrial pacing, either transvenous or transesophageal, is also quite efficacious for terminating these types of tachycardias. Adenosine, although effective in treating orthodromic and antidromic AVRTs, may induce AF in up to 15% of cases and should, therefore, be used with caution. In patients with WPW syndrome, AF is a potentially life-threatening arrhythmia, especially when the accessory pathway has a short antegrade refractory period capable of rapid ventricular conduction.

- (2) **Wide QRS width.** Patients with accessory pathways can present with wide QRS complex resulting from (1) orthodromic AVRT with aberrant conduction; (2) antidromic AVRT; or, **most importantly**, (3) atrial tachycardia/atrial flutter/atrial fibrillation) with antegrade conduction down an accessory pathway. Since it is often initially impossible to determine the mechanism of a wide QRS complex in patients with an accessory pathway, they should be treated with agents that slow conduction in the accessory pathways (procainamide, flecainide, sotalol, or amiodarone). Because atrial arrhythmias with antegrade accessory pathway conduction are **not** AV node-dependent, AV nodal blocking therapies are ineffective and potentially very dangerous. β -Blockers, calcium channel blockers, digoxin, and adenosine should be avoided in patients presenting with wide complex tachycardias (WCTs), as they may encourage preferential conduction down accessory pathways and accelerate ventricular rates, precipitating ventricular fibrillation (VF). **If the tachycardia persists, synchronized DCC** is the treatment of choice. Energies of at least 200 J are likely to be required.
- (3) If the patient develops AF, it has been observed that **definitive therapy for the AV reentrant circuit, such as ablation of the accessory pathway, often results in the prevention of future episodes of AF.**

b. Long-term management

- (1) **Priority of therapy.** Patients whose disease is asymptomatic at diagnosis are at low risk for sudden death. As such, it may not be justified to pursue medical or ablative therapy in these patients unless there is a family history of sudden death or the patients are competitive athletes or are in a high-risk occupation. Patients whose disease is symptomatic or who have a history of AF or aborted sudden death may be at higher risk, and such patients warrant further study.
- (2) **Medical therapy.** Medical therapy may be **appropriate for those with increased risk but no prior symptoms, those with accessory pathways located near the normal conduction pathway that might develop AV block with RFA**, or those at increased risk from invasive procedures. Single-drug therapy may be attempted with **amiodarone, sotalol, flecainide, or propafenone**. These drugs work to slow conduction in both the accessory pathway and the AV node. **Combination therapy** can be accomplished with drugs that work on the AV node (calcium channel blockers, β -blockers) and with drugs that work exclusively on the accessory pathway (class IA antiarrhythmics).
- (3) **Percutaneous therapy.** RFA is effective 85% to 98% of the time, depending on the location of the accessory pathway. Recurrence rates are approximately 5% to 8%. Catheter ablation should be considered for any patient at high risk, patients with symptoms or tachycardias refractory to medical therapy, those who have intolerance to medical therapy, and those with high-risk occupations such as pilots.

J. Atrial premature depolarizations (APDs). APDs are premature depolarizations that arise from a region other than the SN. The P-wave morphology and PR interval may be different from the sinus P wave and normal P interval, depending on the location and timing of the APD.

- 1. Clinical presentation.** APDs are usually asymptomatic and in isolation are considered to be benign. Some patients may feel palpitations or skipped beats. If there is atrial bigeminy with each APD causing AV block, patients may develop symptoms of bradycardia. APDs may trigger SVT (AVNRT, AVRT, and atrial tachycardia) or AF in patients with the electrical and structural substrate for these arrhythmias. APDs increase in frequency as patients age and may be more frequent in patients with mitral valve disease, LV dysfunction, hypertrophic cardiomyopathy (HCM), mitral stenosis, pulmonary disease, and renal failure. Stress, alcohol and caffeine consumption, and smoking can promote APDs. However, APDs also occur in healthy individuals with structurally normal hearts and without significant external exposures (caffeine, alcohol, and stress). Although one study showed a correlation between the frequency of APDs within a 24-hour period and the risk of stroke in men, it is unclear what percentage of these men developed AF. Furthermore, in the ARIC (Atherosclerosis Risk in Communities) study which followed patients with APDs and ventricular premature depolarizations (VPDs), patients with APDs only did not have increased incidence of SCD.
- 2. Pathophysiology.** APDs may be caused by a variety of mechanisms, including reentry, triggered activity, and increased automaticity. Reentry is thought to be the most common mechanism.
- 3. Therapy.** Asymptomatic individuals do not need treatment for APDs. For symptomatic patients, β -blockers and class IA, class IC, and class III antiarrhythmic drugs may be considered, although no randomized controlled trials have been performed in this patient population.

III. VENTRICULAR TACHYARRHYTHMIAS. Ventricular tachyarrhythmias, including monomorphic VT, polymorphic VT, and VF, account for up to 80% of SCD.

A. Ventricular tachycardia. VT is defined as three or more consecutive QRS complexes of ventricular origin at a rate exceeding 100 beats/min. The various types of VTs and their course of disease are discussed in Section IV.

- 1. Clinical presentation.** The presentation is variable and depends on the clinical setting, the heart rate, the presence of underlying heart disease, and other medical conditions. Some patients have no or minimal symptoms, whereas others may present with syncope or sudden death. The loss of normal AV synchrony may cause symptoms in patients with decreased cardiac function at baseline. Heart rates < 150 beats/min are surprisingly well tolerated in the short-term, even in the most compromised individuals. Exposure to these rates for more than a few hours is likely to be associated with heart failure in patients with poor ventricular function, whereas those with normal ventricular function may tolerate prolonged periods at such rates. The range of 150 to 200 beats/min is tolerated variably, according to the factors noted previously. Once the rate reaches and exceeds 200 beats/min, there are symptoms in virtually all patients. **Nonsustained ventricular tachycardia (NSVT)** is generally defined as a VT of duration < 30 seconds. VT is **generally regular in rate and appearance**, although it can be polymorphic in appearance, slightly irregular with respect to rate, and may have capture and/or fusion beats within it.
- 2. Differential diagnosis.** VT needs to be distinguished from **supraventricular tachyarrhythmia with aberrant intraventricular conduction, bundle branch block, and morphologic changes of the QRS complex secondary to metabolic derangement or pacing**.

- a. **Brugada criteria.** Distinguishing VT from **supraventricular tachyarrhythmia with aberrancy** can be challenging. Various criteria have been proposed. A good rule of thumb **is that any WCT in a patient with ischemic heart disease is VT until proven otherwise**. Some have reported that $> 80\%$ of WCTs in such patients are VTs. The **algorithm proposed by Brugada may be helpful in making this distinction, and the algorithm is both sensitive (99%) and specific (96.5%)** in patients without a preexisting bundle branch block. As shown in Figure 21.4, a stepwise approach is applied. In the first step, the precordial leads are examined for the presence or absence of an RS complex. If an RS is uniformly absent, VT is established. If an RS is present in at least one precordial lead, one moves to the second step, which is measuring the interval from the onset of the QRS complex to the nadir of the S wave. If this distance is > 100 milliseconds in at least one precordial lead, then the diagnosis of VT is made. If there is no RS interval > 100 milliseconds, the third step is used. In the third step, one looks for evidence of AV dissociation. If there are more QRS complexes than P waves, then the diagnosis is VT. If not, then one moves to the fourth step, which involves examining the morphology of the QRS in the precordial leads V_1 and V_6 . If the morphology criteria for VT (Fig. 21.5) are present in these leads, then the diagnosis of VT is established. If not, the diagnosis is supraventricular tachyarrhythmia with aberrant intraventricular conduction.
 - b. The Brugada criteria have been further refined to distinguish between VT and supraventricular tachyarrhythmia with antegrade conduction over an accessory pathway. After applying the preceding criteria, a second stepwise algorithm is applied (Fig. 21.6). This **second algorithm has a sensitivity of 75% and a specificity of 100% to diagnose VT and exclude preexcited tachycardia**. In the first step, leads V_4 to V_6 are examined to see if the QRS is predominantly negative. If so, then VT is favored. If not, then the second step, examining leads V_2 to V_6 for the presence of a QR complex in one or more of these leads, is applied. If there is a QR complex in any of these leads, then the diagnosis is VT. The third criterion, presence of AV dissociation, is 100% specific for VT. If there is no AV dissociation, then supraventricular tachyarrhythmia with antegrade accessory pathway conduction is favored.
 - c. A new criterion for differentiating VT from SVT was published in 2008 by Vereckei et al. (1), which boasts a $> 90\%$ accuracy in their cohort (Fig. 21.7). The rationale to use the new method was to simplify the approach by using one electrocardiographic lead (aVR) in a four-step, tree-like model. The method starts with identifying the presence of an initial R wave in aVR. If present, VT is diagnosed. If not, then the next step is to assess the presence of an initial R or Q wave > 40 milliseconds, and if present, is VT. If this criterion is not satisfied, then the presence of a notch on the descending limb of a negative onset and predominantly negative QRS gives the diagnosis of VT. If this is not present, then one should compare the voltage of the initial 40 milliseconds (V_i) with the voltage of the terminal 40 milliseconds (V_t) of the QRS complex. If $V_i/V_t \leq 1$, then it is VT. If none of these criteria are satisfied, then SVT is diagnosed.
3. **Therapy**
 - a. **General management.** The treatment of VT may involve DCC, discontinuation of offending proarrhythmic drugs, specific antiarrhythmic therapy with drugs, correction of electrolyte imbalances, implantable devices, ablation, revascularization, and surgery. The appropriate selection of the preceding therapies is aided by the assessment of the patient, an understanding of the etiology and mechanism of the VT, knowledge of any exacerbating medical conditions contributing to the VT, and the risk-to-benefit ratio of the available therapies.

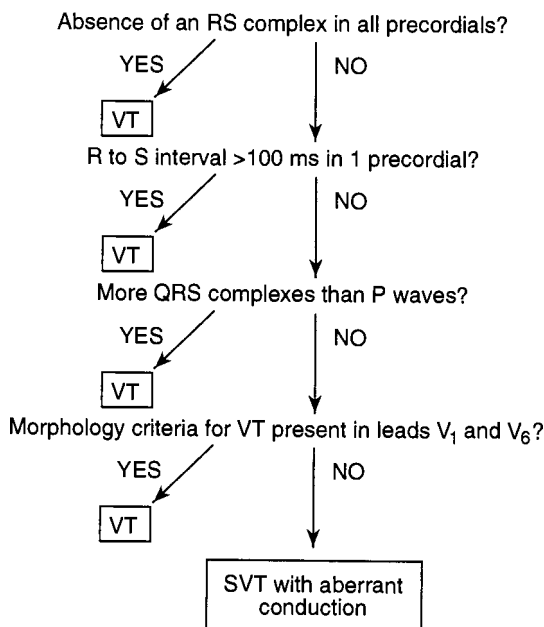


FIGURE 21.4 Brugada criteria for differentiating ventricular tachycardia from supraventricular tachycardia with aberrant intraventricular conduction. VT, ventricular tachycardia; SVT, supraventricular tachycardia.

- b. **Priority of therapy.** A patient who has no hemodynamic compromise can be treated medically, at least initially. As with most types of tachyarrhythmias, **the treatment of any unstable patient with VT is rapid DCC.** The treatment for pulseless VT is asynchronous DCC with a starting energy of 200 to 360 J. If the patient is conscious but has unstable vital signs or is extremely symptomatic, **synchronized DCC** is recommended. Current 2011 Advanced Cardiac Life Support (ACLS) guidelines (AHA) currently emphasize the delivery of high-quality cardiopulmonary resuscitation (CPR): effective chest compressions (100/min and compression depth of at least 2") with minimal interruptions, rescue breaths given over 1 second with visible chest rise while avoiding hyperventilation (30:2 ratio before an advanced airway and 8 to 10 asynchronous breaths/min after airway is secured), and a **single** shock to attempt to defibrillate pulseless VT patients (as opposed to three-stacked shocks) followed by immediate continuation of CPR. (See Section IV.F.3 for treatment of pulseless VT/VF patients.)
- c. **Acute medical therapy.** Intravenous amiodarone, lidocaine, procainamide, β -blockers, and other oral agents may be given initially depending on the clinical scenario. Amiodarone is the agent of choice for resistant VT causing repeated episodes and also for pulseless VT/cardiac arrest. Amiodarone and lidocaine are the preferred agents in patients with LV dysfunction (left ventricular ejection fraction [LVEF] < 40%). Lidocaine is effective when VT is thought to be ischemic in nature. Procainamide is reasonable as the initial treatment in patients with stable monomorphic VT, as it more effectively provides early rate slowing and conversion than amiodarone. β -Blockers may be preferred for acute coronary syndrome, especially if not already being

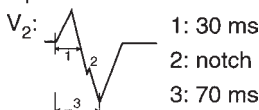
1. QRS width > 0.14 s
2. Superior QRS axis
3. Morphology in precordial leads:

a. RBBB-like pattern



b. LBBB-like pattern

V_1 : RT $>$ RS



V_6 : R/S ratio < 1

V_6 : qR

4. AV dissociation, fusion, capture present

FIGURE 21.5 Classic morphology criteria for ventricular tachycardia.

taken by the patient. Whenever possible, a **reversible cause for VT** should be sought. Elimination of **ischemia** and correction of **electrolyte abnormalities** are recommended. **Bradycardia** may cause frequent premature ventricular contractions or VT. Maneuvers and agents that increase heart rate should be employed for these bradycardias. **Hypotension** should be promptly corrected. Therapy for CHF should be optimized with the agents

Predominantly negative QRS complexes in the precordial leads V_4 to V_6 ?

Yes

No

Certainly VT

Presence of a QR complex in one or more of the precordial leads V_2 to V_6 ?

Yes

No

Certainly VT

AV relation different from 1:1?
(more QRS complexes than P waves?)

Yes

No

Certainly VT

Preexcited
tachycardia

FIGURE 21.6 Brugada criteria for differentiating ventricular tachycardia from antidromic tachycardia over an accessory pathway. VT, ventricular tachycardia; AV, atrioventricular.

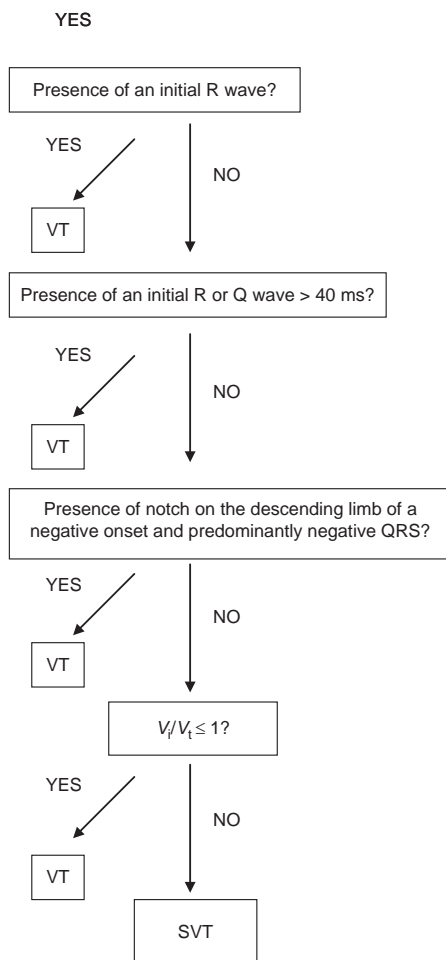


FIGURE 21.7 aVR criteria for diagnosing ventricular tachycardia. V_i = vertical excursion (mV) during initial (V_i) and terminal (V_t) 40 milliseconds of the QRS complex. VT, ventricular tachycardia; SVT, supraventricular tachycardia.

known to promote survival in this disorder. **Offending agents** should be stopped whenever possible, and **antidotes** should be administered in the case of overdose and poisoning.

- 4. Prevention and prophylactic treatment.** All antiarrhythmic agents to date, except β -blockers, have not been shown in randomized clinical trials to be effective as the primary management of patients with life-threatening ventricular arrhythmias or in the prevention of SCD. Since the Cardiac Arrhythmia Suppression Trial (CAST) data have become available, there has been a shift

away from the use of class I agents and toward the **use of class III agents and β -blockers for prophylactic maintenance therapy** of VT. The development of **curative catheter-based therapies and surgical procedures** has somewhat reduced the role of antiarrhythmics in the prevention of recurrence, especially for VT occurring in normal hearts, which has very high cure rates with catheter ablation (**see Section IV.A**). However, antiarrhythmic drug therapy remains the first-line treatment for VT, particularly for patients with cardiomyopathy. The greatest impact on survival in sudden death has been made by the implantable **cardioverter–defibrillator (ICD)**. Data from the Multicenter Unsustained Tachycardia Trial (MUSTT) investigations have shown that **patients with CAD, an EF < 40% and NSVT who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT.

a. Medical therapy

- (1) Although drug therapy continues to have a role in the prevention of VT and sudden death, this role has become more limited as there has been no decrease in mortality with the use of antiarrhythmic drugs. The Electrophysiologic Studies Versus Electrocardiographic Monitoring (ESVEM) trial studied the efficacy of seven antiarrhythmics (imipramine, mexiletine, pirmenol, procainamide, propafenone, quinidine, and sotalol) in preventing the recurrence of sustained VT. Sotalol was seen to be the most effective, although even with sotalol the recurrence rate was disappointing. The European Myocardial Infarct Amiodarone Trial (EMIAT) and the Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) investigations were designed to study the effectiveness of empiric amiodarone for the prevention of VT after MI. Although both of these trials showed a decrease in arrhythmic deaths, no survival benefit was recorded.
- (2) **Combination therapy.** Drug therapy is becoming **an adjunct to ICD therapy** in this high-risk population. At present, fully half of those with ICDs remain on antiarrhythmic therapy. The rationale for this combined therapy includes preventing atrial tachyarrhythmias and reducing the frequency of VT and thus the frequency of ICD discharge.
- (3) Calcium channel blockers are used primarily in the management of supraventricular tachyarrhythmia. However, some of the idiopathic monomorphic VTs, described in Section **IV.A** (the VTs originating in the right ventricular outflow tract [RVOT]), fascicular VT, and the VTs of digitalis toxicity are responsive to calcium channel blocking agents such as verapamil and diltiazem (due to the underlying mechanism of calcium-dependent triggered activity). RFA is potentially curative for idiopathic VTs and should be considered despite effective termination with calcium channel blockers.
- (4) β -Blockers may be effective, particularly for outflow tract VT. Idiopathic left VT may respond to calcium channel blockers.

b. Percutaneous therapy

- (1) **ICDs.** Two large trials comparing ICDs with amiodarone in high-risk patients with prior infarction, the Multicenter Automatic Defibrillator Implantation Trial (MADIT) and the Antiarrhythmics Versus Implantable Defibrillator (AVID) trial, have been completed. High risk implies either an EF of 35% or less or the presence of inducible sustained VT at electrophysiologic study. Both trials showed a **decided advantage for ICDs**, with 30% to 50% reductions in mortality with ICDs. In fact, the AVID trial found no survival benefit from amiodarone, β -blockers, or any other antiarrhythmic agent. Newer ICDs often have antitachycardia pacing (ATP) capabilities, can recognize monomorphic ventricular

rhythms with rates < 200 beats/min, and can rapidly pace the ventricles to restore sinus rhythm, aborting the need for countershock (see Chapter 23). In the Primary Prevention Parameters Evaluation (PREPARE) study which evaluated the effects of ICD programming in a patient population receiving ICDs for primary prevention, using ATP as first-line therapy for fast VT (≥ 182 and < 250 beats/min), including a monitoring zone at 167 beats/min, and applying SVT versus VT discriminators for rates < 200 beats/min helped in reducing shocks without negatively affecting the mortality. Data from MADIT II have shown that in patients with a prior MI and an EF < 30%, the implantation of a defibrillator is associated with a significant improvement in survival.

- (2) **Catheter-based therapy.** RFA may be effective for reducing the incidence of VT. The success rate depends on the type of VT, with the highest success rates (> 90%) in structurally normal hearts. VT associated with underlying cardiomyopathy has lower success rates with ablation, particularly those with arrhythmogenic RV cardiomyopathy and ischemic cardiomyopathy. However, catheter ablation still remains an effective and feasible approach, even for these types of VTs. Presently, catheter ablation of VT does not obviate the need for an ICD in a patient with an indication for one.

IV. DIAGNOSTIC EVALUATION OF A PATIENT WITH VT. Once the diagnosis of VT has been established and the patient has been acutely managed with either DCC or medical therapy, further management depends on the underlying cardiac pathology. In broad terms, the substrate can be divided into two categories: the structurally normal heart and the structurally abnormal heart. Various modalities are available to determine the cardiac structure and function, which include electrocardiography, cardiac catheterization, echocardiography, nuclear imaging, and magnetic resonance imaging.

- A. **VT in a structurally normal heart.** About 10% of VT in the United States occurs in structurally normal hearts, the so-called idiopathic VT. These patients have no significant CAD, no family history of arrhythmia or sudden death, and normal surface ECGs. They can be focal VTs or reentry VTs. Focal VTs are a result of triggered activity, abnormal automaticity, or reentry within the Purkinje fibers.

1. **Focal VT**

- a. **Mechanism.** Focal VTs most commonly arise from the RVOT and account for up to 70% of idiopathic VTs. They may be caused by cAMP-mediated EADs. Of particular importance in the diagnosis of a patient who presents with LBBB VT is to be cognizant of the possibility of arrhythmogenic right ventricular dysplasia (ARVD), which falls into the category of VT/PVCs in the structurally abnormal heart. The clinician should investigate for RV structural abnormalities (fatty infiltration), ask about a family history of ARVD, and review the electrogram for the presence of T-wave inversion across the right precordial leads, and/or epsilon waves (Fig. 21.10). A cardiac MRI or cardiac PET scan may also be useful to rule out the presence of cardiac sarcoidosis, which also would fall into the category of the structurally abnormal heart.
- b. **ECG.** The surface ECG usually demonstrates an LBBB and inferior axis with very positive QRS voltage in inferior leads. Other locations of focal VTs may include the LV outflow tract, aortic cusps, pulmonary artery, mitral and tricuspid annuli, papillary muscles, and epicardium.
- c. **Treatment.** In general focal VTs are benign, carrying a very low risk of SCD. Therefore, the treatment is predominantly guided by symptoms. Given the role of cAMP in inducing this form of VT, adenosine may be effective at acute termination. For longer term therapy in the symptomatic patient,

β -blockers are typically the first-line agents and can be effective in up to 50% of patients. The nondihydropyridine calcium channel blockers may also be effective in 25% to 50% of patients. Very effective medications are sotalol and amiodarone, with up to 90% success rate in eliminating symptoms, but potential side effects may limit their use. Patients who wish to potentially avoid lifelong medications or who are refractory to medical therapy can be considered for ablation, which has variable success rate depending on the location. RVOT VT ablation success rate may be as high as 90%. Ablation procedures, while generally safe, may be associated with infrequent but life-threatening complications, including cardiac perforation and tamponade.

2. **Fascicular VTs.** Fascicular VT involves reentry using the tissue of the LV septum as the antegrade limb and usually the posterior fascicle in the retrograde limb.
 - a. **ECG.** This typically produced a right bundle branch block (RBBB) with left-axis deviation pattern. Less commonly, the QRS pattern is an RBBB with right-axis deviation (left anterior fascicular VT).
 - b. **Treatment.** This subtype of VT may be verapamil-sensitive, but catheter ablation can be attempted in patients who want to avoid long-term medication or in whom medical therapy is ineffective.
- B. **VT/VF associated with channelopathies.** Various cardiac ion channel disturbances can predispose to ventricular arrhythmias. Patients with these channelopathies have no overt structural heart disease. They are genetically heterogeneous and have variable penetrance. They include LQTS, short QT syndrome, Brugada syndrome, and catecholaminergic polymorphic VT.

1. **Long QT syndrome**

- a. **Pathology and presentation**

This channelopathy is characterized by prolonged cellular repolarization resulting in an increase of the QT interval. Clinical presentation includes syncope or sudden death as a result of torsade de pointes, and usually an autosomal dominant transmission pattern.

While at least 12 mutations have been identified, the most common subtypes of LQTS are LQT1, LQT2, and LQT3, which are characterized by mutations in the I_{K^2} , I_{K^2} , and I_{Na} channels, respectively. Interestingly, a minority of patients with the genetic mutation may actually have “normal” QT intervals. LQT1 and LQT2 mutations result in decreased outward potassium current, while LQT3 mutation results in increased inward sodium current, both of which result in prolonged cellular repolarization. The Jervell and Lange-Nielsen, a clinical syndrome with a constellation of a prolonged QT and sensorineural deafness, is transmitted in an autosomal recessive pattern, and thus far has been localized to the LQT1 or LQT5 mutations.

LQT1 patients typically have broad-based T waves and exercise-induced arrhythmias, especially during swimming. LQT2 syndrome is characterized by low-amplitude or notched T waves and auditory triggers such as sudden loud sounds like alarm clocks or strong emotion, and LQT3 is characterized by a long isoelectric ST segment and arrhythmias during sleep.

- b. **Treatment**

In patients with LQTS, risk stratification involves assessment of age, gender, clinical history, and possibly the QT interval and genetic mutation. While β -blockers have a variable efficacy depending on the type of LQT mutation, typically high doses of propranolol or nadolol are used to prevent clinical symptoms. For the LQT3 patients, there may be a role for flecainide given its effects on the sodium channel inhibition, but this is experimental and has not reached guideline recommendations yet. Patients should be advised against high-intensity sports and should be educated regarding avoidance of QT prolonging drugs. Patient with syncope, history of aborted

sudden death, or torsade de pointes despite β -blocker therapy should undergo ICD implantation. Certain high-risk subgroups such as patients with LQT3 in whom β -blockers may be less effective, patients with QTc > 550 milliseconds, or female LQT2 patients with QTc > 500 milliseconds may benefit from ICD implantation. Left cardiac sympathetic denervation can be used as an adjunctive therapy to reduce recurrence of arrhythmias.

2. **Short QT syndrome.** This syndrome is characterized by gain-of-function mutations in the I_{Ks} , I_{Kr} , and I_{K1} potassium channels or CACNA1 and CACNB2 L-type calcium channel mutations. ICD therapy is the primary treatment modality. However, particular attention needs to be given to the prevention of inappropriate shocks, as patients may have T-wave oversensing (tall T waves) and a high incidence of AF.
3. **Brugada syndrome.** Brugada syndrome is a condition associated with SCD in the setting of a structurally normal heart, characterized by an electrocardiographic pattern of RBBB and ST-segment elevation in leads V_1 to V_3 (Fig. 21.8). It is inherited in an autosomal dominant pattern with a male predominance. It is a genetically heterogeneous disease with many mutations linked to the gene *SCN5A*, which encodes for a cardiac sodium channel, leading to unopposed I_{Na} potassium current in the RV epicardium. The diagnosis can be difficult because of the variable expression of the ECGs at baseline, changes in the ECG over time induced by a host of factors (temperature, heart rate, autonomic tone, and medications), and the wide range of clinical manifestations. The diagnosis should be considered in patients who have documented VF, self-terminating polymorphic VT, family members with ST-segment elevation, syncope, or family history of sudden death in the setting of the electrocardiographic findings noted previously. Currently, no medication has proved effective in preventing SCD in these patients, but quinidine, which blocks the I_{Na} channel, may be used as an adjunctive therapy to reduce the likelihood of arrhythmias. ICDs are currently the only available treatment and are recommended in patients with previous cardiac arrest (class I), syncope with spontaneous ECG pattern (class IIa), and documented VT that has not resulted in cardiac arrest (class IIa). It is generally recommended to implant an ICD in **symptomatic** patients and clinically follow **asymptomatic** patients with an abnormal ECG only on pharmacologic provocation and no inducible ventricular arrhythmias.
4. **Catecholaminergic polymorphic VT.** This arrhythmia is more common in adolescents and children and may present with SCD or stress-induced syncope. While usually familial, it can also occur due to de novo mutations. Triggers often include emotional or physical stress, and the arrhythmia can be polymorphic, bidirectional, and less commonly, VF. Two culprit genes have been identified thus far: calyculin 2 (autosomal recessive pattern) and cardiac ryanodine receptor (autosomal dominant pattern). ICDs are indicated in patients with this syndrome and syncope and/or VT. β -Blockers can reduce the incidence of arrhythmias as well. Flecainide and sympathetic denervation have been used in some patients who are refractory to β -blocker therapy.

C. VT in the structurally abnormal heart

1. **Ischemic VT.** Patients with ischemic VT may have acute ischemia leading to MI or a history of ischemic heart disease with scar. Patients who have VF/VT within 48 hours of an acute MI have a relatively high in-hospital and 30-day mortality compared with patients who do not have VF/VT.
 - a. **Etiology and pathophysiology.** At the cellular level, ischemia may alter action potentials, prolong refractoriness of cells, and uncouple the cell-to-cell propagation of depolarization. The biochemical milieu in which the cells exist with respect to ion concentrations, acid-base balance, and so forth can be altered. Also, the myocardial damage as a result of infarction is structurally

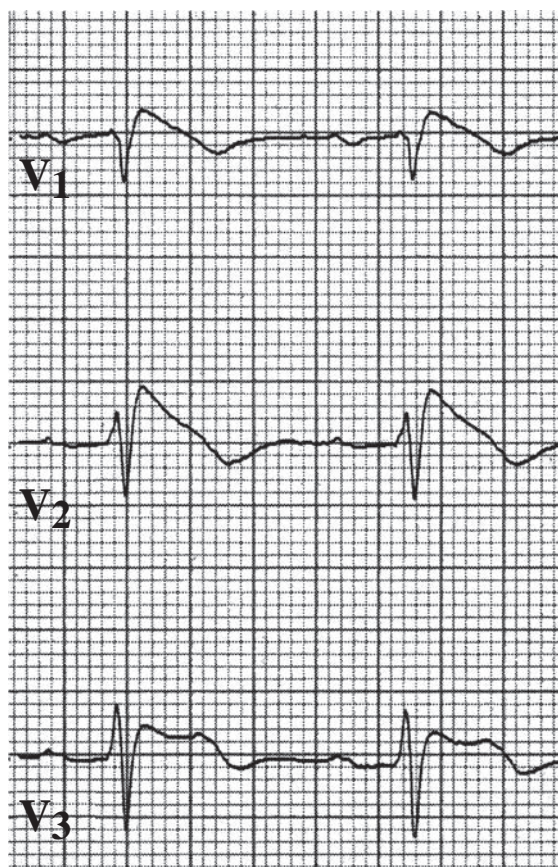


FIGURE 21.8 Leads V_1 through V_3 , demonstrating Type 1 Brugada pattern.

heterogeneous. Therefore, scar tissue and healthy tissue are admixed in the region of the infarction. As described before, a reentrant circuit requires two functionally distinct pathways with unidirectional block in one pathway and slowed conduction down a second pathway. The changes associated with ischemia provide the anatomic substrate for reentry. The VT in the setting of ischemia tends to be **polymorphic**, while VT in the setting of established myocardial scar tends to be **monomorphic**. Ischemia has been shown to prolong the QT interval in some subjects, often with associated T-wave inversion. The **QT interval in ischemic-mediated polymorphic VT is not as prolonged** as that in torsade de pointes, another polymorphic VT. Ischemia is by far the **most common cause of polymorphic VT with normal QT interval**.

- b. **Predictors of VT.** As might be expected, **larger infarcts with greater resultant impairment of LV systolic function** are more likely to be associated with VT. In fact, LV systolic function is the single most important predictor of sudden death due to arrhythmia. Similarly, the presence of an **open artery**

- appears to reduce the occurrence of VT and other arrhythmias.** Other proposed predictors include syncope, abnormal signal-averaged electrocardiogram (SAECG) result, NSVT, absence of heart rate variability, abnormal electrophysiologic study outcome, and T-wave alternans (TWA); however, currently, the LVEF remains the most accurate predictor of sudden death.
- c. **Laboratory examination and diagnostic testing.** The various tests for risk stratification (electrophysiologic study, SAECG, heart rate variability, TWA, and so forth) have shown poor specificity and positive predictive value for VT **and thus should not be used alone to guide therapy but in combination with the rest of the clinical information.**
 - d. **Role for ICD.** In patients who present with a VF/VT arrest in the setting of an acute MI (within 24 to 48 hours of infarction), revascularization should be the primary initial treatment. Given the fact that acute ischemia is considered a “transient or potentially correctable cause” of VF/VT, and such patients were excluded from the AVID trial, based on currently guidelines, an ICD would be indicated 90 days after revascularization if the LVEF is $\leq 35\%$ or after 40 days if no revascularization was performed, but treatment should be guided on a patient-to-patient basis. Of note, patients in the AVID registry who were excluded from the AVID trial due a “transient or potentially correctable cause” had a high mortality risk in follow-up. Of the 278 patients studied, 183 patients were determined to have ischemic causes. Of these, 161 were categorized as new myocardial infarction and 22 were categorized as transient ischemia. Other causes included electrolyte abnormalities, antiarrhythmic drug interaction, and “other (illicit drug use, sepsis, hypoxia, electrocution, drowning)”. For patients who are post-MI and are deemed to be at high risk for SCD during the waiting period of 40 to 90 days, a wearable cardioverter-defibrillator (WCD) may provide protection against cardiac arrest, but no randomized clinical trials comparing WCDs with medical therapy in this post-MI period have been completed to date. Patients with late VT/VF (i.e., > 48 hours after acute MI) are deemed to be particularly high risk for recurrent VT/VF and therefore typically receive ICDs before hospital discharge. These patients are considered to meet secondary prevention indications for ICDs.
 - e. Accelerated idioventricular rhythm (Fig. 21.9) is a form of VT seen almost exclusively in ischemic heart disease, particularly during an MI and especially after reperfusion of an occluded territory. It may be seen with digitalis toxicity, but can also be present in healthy adults and children with no structural heart disease.
 - (a) The electrocardiographic features include regular or slightly irregular ventricular rhythm, rate of 60 to 110 beats/min, a QRS morphology resembling that of PVCs, and, often, AV dissociation as well as fusion beats and capture beats.
 - (b) **Pathophysiology.** The ectopic ventricular pacing focus competes with the SN and takes control of the ventricular rate when the sinus rate slows or when sinoatrial or AV block occurs. Enhanced automaticity is the likely underlying mechanism.
 - (c) Accelerating the sinus rhythm with atropine or atrial pacing can be useful to suppress the accelerated idioventricular rhythm. **Therapy is rarely necessary, unless** the loss of AV synchrony results in hemodynamic compromise, a more rapid VT intervenes, the accelerated idioventricular rhythm falls on the T wave of the preceding beat (R on T phenomenon), the ventricular rate is rapid enough to produce symptoms, or VF occurs.
2. **Dilated cardiomyopathy (DCM).** Risk stratification is particularly difficult in patients with DCM as SAECG, microvolt TWA, and an electrophysiologic study are not reliable predictors in this population, and asymptomatic ventricular arrhythmias are common. The **Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation** (DEFINITE) and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) have influenced the current guidelines for implanting ICDs in patients with DCM. ICDs are recommended for patients

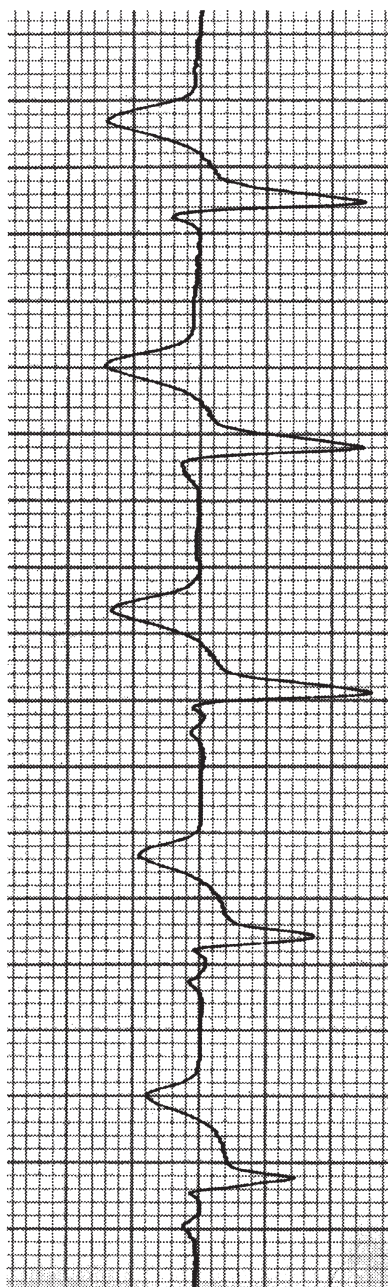


FIGURE 21.9 Accelerated idioventricular rhythm (beats 3 through 5), interspersed with normal sinus rhythm (beats 1 and 2), lead IV.

who manifest life-threatening arrhythmias or syncope and for primary prevention in patients who have an LVEF < 35% and are New York Heart Association (NYHA) classes I–III (less evidence exists for class I). All patients should be receiving chronic optimal medical therapy and have a life expectancy > 1 year. Bundle branch reentrant tachycardia occurs most commonly in patients with DCM for which electrophysiologic testing is helpful in diagnosing and guiding ablative treatment. Although ablation may be curative if bundle branch reentry is the mechanism, such patients should still be considered for ICD implantation.

3. **Hypertrophic cardiomyopathy.** Supraventricular tachyarrhythmia and AF are particularly poorly tolerated by these patients, as is ischemia, and may lead to VT. No prospective randomized trials regarding ICD therapy have been carried out to date in this patient population. Consequently, the precise risk stratification is debated. ICDs are recommended for patients who have sustained VT or VF, or both, and for primary prevention in patients who have either one of the preceding life-threatening arrhythmias or one or more of other major risk factors for SCD (nonsustained spontaneous VT, family history of premature SCD, unexplained syncope, LV thickness ≥ 30 mm, or abnormal exercise blood pressure). Again, all patients should be receiving chronic optimal medical therapy and have a life expectancy > 1 year. Electrophysiologic study may be helpful in stratifying risk for VT and sudden death. Patients at low risk for HCM include those with infrequent or brief episodes that are asymptomatic or mildly symptomatic. Although **amiodarone** may be beneficial in this population, an ICD is increasingly used in those considered to be at high risk.
4. **Muscular dystrophies**, particularly Duchenne's muscular dystrophy and myotonic dystrophy, have been associated with frequent defects in the conduction system. Heart block and bundle branch block as well as sudden death due to ventricular tachyarrhythmias are well-recognized complications of these muscular disorders.
5. **Congenital heart disease.** Structural abnormalities such as **repaired tetralogy of Fallot and mitral valve prolapse** have been associated with increased risk of VT and sudden death. In tetralogy of Fallot, the VT often originates in the RVOT, at the site of a previous repair. Risk of VT and sudden death in this population has been associated with QRS width (and rate of QRS width increase) as well as severity of pulmonary insufficiency. Mitral valve prolapse has been uncommonly linked to sudden death, although ventricular arrhythmias are not uncommon. **The prognosis with respect to VT is quite good in mitral valve prolapse.**
6. **Arrhythmogenic right ventricular cardiomyopathy** is a cardiomyopathy that begins in the right ventricle and often progresses to involve the left ventricle. It results in RV dilation with resultant poor contractile function. The RV muscle becomes increasingly replaced by adipose and fibrous tissues as the disease progresses. VT arising in the right ventricle is often an early manifestation of this disorder. The **VT is a reentrant type and has an LBBB morphology**, although in sinus rhythm there is often inversion of the T waves in the anterior precordial leads and a slurring of the terminal portion of the QRS complex, known as an epsilon wave (Fig. 21.10). These patients frequently have a positive SAECG for late potentials. The combination of the scarring and the late potentials provides the anatomic substrate for reentry. During electrophysiologic study, it may be possible to elicit VT of varying morphologies, due to the prolific scarring of the myocardium. The **risk of VT correlates with the extent of myocardial involvement.** Therapy with sotalol or high-dose amiodarone may be somewhat successful. Ablation via catheters is often successful, but only temporizing, as the generalized involvement tends to give rise to arrhythmias at a different locus later in the disease course. ICDs are often the only reliable therapy to prevent sudden

death in this disorder. Patients are advised against intense exercise, as this may promote the incidence and progression of arrhythmias.

7. Several inflammatory or infectious conditions have been associated with VT.
 - a. Sarcoidosis is frequently cited as a cause of heart block and may also cause VT and VF. **Amiodarone** and **sotalol** are the most efficacious agents in this disorder, although an ICD may be necessary in addition to the drug therapy.
 - b. Acute myocarditis has been associated with both polymorphic and monomorphic VTs. It may be intractable in giant cell myocarditis. **Antiarrhythmic therapy and anti-inflammatory therapy** are generally combined in the treatment of these patients.
 - c. Chagas disease, caused by the parasite *Trypanosoma cruzi*, is a well-known cause of cardiomyopathy, particularly in South and Central America. VT and other arrhythmias due to conduction system involvement are common complications. Therapy involves antiparasitic treatment, standard therapy for CHF, antiarrhythmics, and pacemaker or ICD implantation, as appropriate. Some patients require catheter ablation of refractory VT, which sometimes must be performed epicardially.
8. **Coronary anomalies.** Anomalous aortic origin of the coronary artery is recognized as a cause of sudden death and/or exercise-induced death in young individuals. In an autopsy study of over 200 patients conducted by the Armed Forces Institute of Pathology, the most common coronary anomalies included the right coronary artery and left main coronary artery arising from the left sinus, the left main and right coronary arteries arising from the right sinus, single coronary artery from the aorta, and the left main or left anterior descending artery arising from the pulmonary artery. Patients whose coronary arteries take an interarterial course (between the pulmonary artery and the aorta) may develop exercise-induced ischemia and/or sudden death. Surgical revascularization in patients with symptomatic coronary anomalies has been well described. Surgical treatment for patients with high-risk coronary anomalies who are asymptomatic is controversial.

D. Drug-induced VT. Drugs are a well-known cause of VT, both polymorphic and monomorphic VTs. This is particularly true in ischemic or infarcted hearts. Phenothiazines, tricyclic antidepressants, digitalis, epinephrine, cocaine, nicotine,

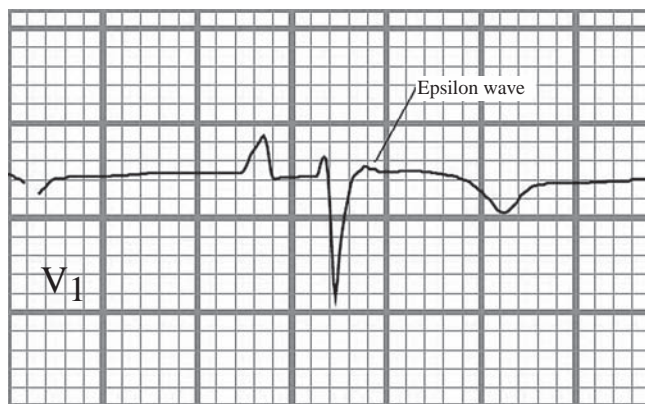


FIGURE 21.10 Epsilon wave in a patient with arrhythmogenic right ventricular dysplasia.

alcohol, and glue (inhaled) are some of the wide variety of drugs that have been implicated in the development of monomorphic VT. The CAST and other trials of the late 1980s showed an increase in mortality resulting from the use of class I antiarrhythmic agents employed to suppress asymptomatic ventricular ectopy after MI. NSVT and depressed LV function remain risk factors for sudden death, and the agents studied in CAST did decrease the occurrence of ventricular ectopy; however, it is believed that these drugs (flecainide, encainide, and moricizine) generated VT, causing sudden death in recipients. These agents all have in common their sodium channel blocking activities. Other drugs in this class, including procainamide, quinidine, disopyramide, lidocaine, tocainide, and mexiletine, have all been shown either experimentally or clinically to be associated with increased mortality compared with controls in the periinfarction period. The results of CAST caused a major shift away from the sodium channel blocking agents (class I antiarrhythmics) in the periinfarction period.

1. The generation of torsade de pointes due to effects on the QT interval is discussed in Section IV.D.2.
2. Digitalis toxicity can propagate DADs, which generate action potentials, leading to VT. The VT of digitalis toxicity is typically monomorphic and often responds to calcium channel blockers. Rarely, digitalis toxicity manifests as a bidirectional VT, meaning that it has a regular rhythm with an axis that alternates from -60° to -90° to $+120^\circ$ to $+130^\circ$, with a ventricular rate from 140 to 200 beats/min. Because digitalis toxicity may have a narrow QRS complex and may respond to calcium channel blockers, it may be confused with supraventricular tachyarrhythmia. This type of VT is best managed by removing the offending agent, digoxin, with its binding antibody. The treatment for digitalis toxicity is the same in the face of bidirectional VT.
 - a. Torsade de pointes is a type of polymorphic VT associated with delayed myocardial repolarization, most often manifested as a prolonged QT interval. Although the duration of torsade de pointes is typically brief (< 20 seconds), it can be sustained and can degenerate into VF. It generally has an irregular ventricular rate (> 200 beats/min) and displays a polymorphic structure with an undulating appearance. The QRS complexes appear to twist around an isoelectric axis. Characteristics that distinguish torsade de pointes from other forms of VT include (1) prolonged QT interval, (2) initiation with a short–long–short sequence, and (3) typical “twisting of the points” appearance of the VT.

(1) **Etiology.** QT prolongation can be congenital or acquired.

- (a) The **congenital** forms are seen in the LQTS, discussed in Chapter 23.
- (b) The **acquired forms are most often drug induced**, although polymorphic VT with a prolonged QT can be caused by electrolyte abnormalities, hypothyroidism, cerebrovascular events, MI or ischemia, starvation diets, organophosphate poisoning, myocarditis, severe CHF, and mitral valve prolapse.

The **most commonly implicated drugs have been the class IA drugs**, although less frequent occurrences have been reported with all subclasses of class I antiarrhythmics. The class III drugs, such as sotalol, dofetilide, and, less commonly, amiodarone, have been implicated. The incidence of torsade de pointes with sotalol is in the range of 2% to 5% and with dofetilide it is $< 1\%$. Ibutilide is an antiarrhythmic agent for supraventricular tachyarrhythmias that is associated with an incidence of torsade de pointes at least as high as that of sotalol. Other drugs implicated include the phenothiazines, haloperidol, and the tricyclic antidepressants. Antibiotics, including erythromycin and other macrolides, as well as trimethoprim–sulfamethoxazole combinations, have been implicated. The macrolides are particularly prone to cause torsade de pointes when combined with certain antihistamines such

as astemizole and terfenadine. These antihistamines have also been found to cause torsade de pointes when combined with certain azole antifungal agents such as ketoconazole. Ionic contrast and promotility agents such as cisapride have also been associated with torsade de pointes. Medications associated with increasing QT interval are listed on the following website: www.torsades.org. It is maintained by the University of Arizona Center for Education and Research on Therapeutics.

Bradycardia can promote torsade de pointes in patients with prolonged QT intervals, although it is not clear if bradycardia by itself predisposes to torsade de pointes. Specifically, pause-dependent VT occurs in the setting of bradycardia and a prolonged QT interval. Usually a long RR interval followed by a short RR interval followed by another long RR interval initiates the VT.

Electrolyte disorders. **Hypokalemia** is the electrolyte disorder most reliably linked to torsade de pointes. **Hypomagnesemia** has been proposed as a logical cause, as the administration of magnesium frequently terminates torsade de pointes. However, there is scant evidence to confirm this. Likewise, although **hypocalcemia** is associated with prolongation of the QT interval, there are only rare reports of torsade de pointes associated with hypocalcemia.

Short coupled VT. Polymorphic VT is initiated < 400 milliseconds following the preceding QRS complex.

R-on-T phenomenon occurs when a defibrillation or pacing current or spike is delivered simultaneously with occurrence of the electrocardiographic T wave resulting in polymorphic VT.

A variety of **cerebrovascular events** have been associated with torsade de pointes, most notably subarachnoid hemorrhage. The prolongation of the QT interval sometimes seen with intracranial bleeding is usually transient, resolving within weeks.

(2) Therapy. Acute management is aimed at terminating the arrhythmia.

- (a) If torsade de pointes is sustained or associated with hemodynamic compromise, prompt DCC should be carried out. Starting voltages are generally 50 to 100 J and can be advanced to 360 J if necessary.
- (b) Correction of hypokalemia, hypomagnesemia, and hypocalcemia should be undertaken promptly. Magnesium can be given in a bolus form at a dose of 1 to 2 g, with a total dose of 2 to 4 g given over 10 to 15 minutes. This successfully terminates torsade de pointes within 5 minutes in up to 75% of patients and within 15 minutes in virtually all patients.
- (c) Bradycardia can be corrected with either isoproterenol infusion or temporary transvenous pacing. Pacing may be preferable when readily available, due to the potential complications of isoproterenol therapy (worsened ischemia and hypertension). Offending agents should be discontinued.

E. Miscellaneous

Commotio cordis. Commotio cordis is the sudden ventricular arrhythmia occurring as a result of a blunt, nonpenetrating impact to the precordial region, which is most commonly observed in young healthy persons during participation in sports. The blow likely falls within a small 10- to 30-millisecond window of ventricular vulnerability just prior to the peak of the T wave that results in polymorphic VT and sudden death. A 2002 case series of 128 individuals showed that only 16% of patients survived an episode of commotio cordis, with most returning to a baseline level of function. Prompt CPR/defibrillation was the only identifiable factor associated with a favorable outcome.

F. Ventricular fibrillation

1. VF is a **chaotic ventricular rhythm that reflects no organized electrical activity and hence no cardiac output** from the ventricle. It is devoid of the distinct elements that makeup the usual electrical complex of ventricular activity. It is a **rapidly fatal rhythm, and if resuscitation is not begun within 5 to 7 minutes, death is virtually certain**. VF is often preceded by VT. Virtually all of the risk factors and conditions discussed for VT are applicable to VF. It may arise without any inciting cardiac rhythm or event.
2. **Course of disease.** Of patients who experience an out-of-hospital cardiac arrest, 75% have VF as their initial cardiac rhythm. Of those successfully resuscitated, 75% have significant CAD and 20% to 30% have a transmural infarction. Patients without an ischemic etiology have an increased risk of further episodes of sudden death, whereas those who have an MI associated with sudden death have a 1-year recurrence rate of 2%. Anterior MI complicated by VF represents a subgroup at high risk for recurrence of sudden death. Predictors of SCD include evidence of ischemia, decreased LV systolic function, 10 or more PVCs per hour on telemetry, inducible or spontaneous VT, hypertension and LV hypertrophy, smoking, male sex, obesity, elevated cholesterol, advanced age, and excessive alcohol use.
3. **Therapy.** As noted previously, VF is a rapidly fatal rhythm, which virtually never terminates spontaneously. CPR must be initiated promptly and rapid, asynchronous DCC performed as soon as possible. A **single** shock of 200 to 360 J (biphasic devices, 200 J; monophasic devices, 360 J) should be given initially followed by immediate resumption of CPR for 2 minutes before checking for a pulse. If VF/pulseless VT persists, an immediate **second** shock (biphasic devices, ≥ 200 J; monophasic devices, 360 J) should be given followed by a vasopressor (1 mg of epinephrine every 3 to 5 minutes; single dose of 40 units of vasopressin may replace first or second dose of epinephrine). If VF/pulseless VT persists after two or three shocks, CPR, and a vasopressor, administration of an antiarrhythmic should be considered (amiodarone is preferred and lidocaine as an alternative). The emphasis should be on performing high-quality CPR with interruptions in chest compressions **only** for ventilation (until an advanced airway is established), rhythm checks (pulse checks only if an organized rhythm is observed), and shocks.

See Chapter 23 for a discussion about the long-term treatment of survivors of VF.

G. Ventricular premature depolarizations and nonsustained ventricular tachycardia.

1. **VPDs** are common in patients with both structurally normal and structurally abnormal hearts. They are usually not hemodynamically significant, except in patients with depressed EF or in patients with frequent VPDs and/or bradycardia. Whether or not VPDs increase risk of subsequent cardiovascular events depends on the study. In the ARIC study, after controlling for cardiovascular risk factors, patients with a single VPD on a 2-minute Holter had over a two-fold incidence of dying of CAD over a 10-year follow-up period compared with patients who had no VPDs. However, in the Baltimore Longitudinal Study on Aging which evaluated ambulatory ECGs on apparently healthy subjects ≥ 60 years of age, VPDs on ambulatory ECG monitoring did not predict the development of coronary events. One main difference between the ARIC study and the Baltimore Longitudinal Study was that in the latter, inclusion criteria were more strict, requiring a normal exercise stress test, and therefore, likely had less patients with subclinical CAD.

Although patients post-MI with VPDs have a higher mortality than patients post-MI without VPDs, suppression of VPDs with antiarrhythmic medication is associated with increased mortality. For patients with symptomatic VPDs, β -blockers or calcium channel blockers should be the first-line agent. If this fails and the patient has no structural heart disease, class IC

agents may be effective; however, potential risks and benefits of the antiarrhythmic drug should be explained to the patient. Sotalol has been shown to reduce the frequency of VPDs by 70% to 80%. In CAMIAT, amiodarone reduced VPDs and arrhythmic deaths, but did not reduce overall mortality. **A very high burden of VPDs (> 20,000/d) may be associated with reduced EF, although it may be difficult to determine if the VPDs caused the cardiomyopathy or vice versa.** However, in some patients with a high burden of VPDs and idiopathic DCM, treating the VPDs either with medication or with catheter ablation may improve the LVEF. Ablation can be an alternative approach to treatment in patients with very symptomatic VPDs refractory to medical therapy and/or patients with reduced EF thought to be a result of the VPDs.

2. **NSVT** is defined as VT of duration < 30 seconds. It can occur in up to 4% of healthy adults and increases in frequency as people age, and NSVT during exercise is not associated with a poor cardiovascular prognosis. The approach to NSVT is based on the cardiac substrate. However, patients with frequent polymorphic NSVT should undergo an evaluation for LQTS and catecholaminergic VT (Sections **IV.B.1** and **IV.B.4**, respectively). One should also be mindful of repetitive monomorphic NSVT that may be of LBBB morphology in patients who have a family history of arrhythmias or sudden death, which may suggest ARVD. Monomorphic NSVT may also be a part of the spectrum of the outflow tract VTs (Section **IV.A.1**).
 - a. In patients in whom structural heart disease has been excluded, NSVT does not carry prognostic significance. Treatment should therefore only be guided by symptoms. A similar approach to NSVT with regard to medication choices is used as with symptomatic VPDs (Section **IV.G.1**.)
 - b. Structural heart disease. In patients with MI, NSVT within the first 24 to 48 hours has little prognostic significance. However, NSVT > 48 hours after acute MI may increase the risk of sudden death by almost twofold, and the risk is even higher in patients with reduced LV function. **Patients with CAD, an EF < 40%, and NSVT who have inducible sustained VT on testing are at substantially increased risk** over those who do not have inducible VT. In patients with HCM, NSVT on Holter monitoring is one of the major risk factors of SCD. Patients with mitral valve prolapse and aortic stenosis who have NSVT are not at increased risk for SCD compared with those without NSVT. In patients with nonischemic DCM, NSVT is not an independent predictor of sudden death.

ACKNOWLEDGMENTS: *The author thanks Drs. Ross Downey, Keith Ellis, and Thomas Dressing for their contributions to earlier editions of this chapter.*

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Bradyarrhythmias, Atrioventricular Block, Asystole, and Pulseless Electrical Activity

I. INTRODUCTION. Bradyarrhythmias and **conduction blocks** are common electrocardiographic findings. Many of these arrhythmias are asymptomatic and do not require specific therapy, whereas others can be life threatening, requiring rapid intervention. **Myocardial ischemia** is an important cause of acute and potentially dangerous bradyarrhythmia.

II. ANATOMY

A. Sinoatrial node. The sinus beat originates in the **sinoatrial (SA) node**, a focus of automatic cells near the junction of the superior vena cava and right atrium.

1. The blood supply to the SA node is from the **sinus node artery**, which arises from the proximal **right coronary artery** in 55% of the population (Fig. 22.1) and from the **circumflex artery** in 35%. The SA node receives a dual supply of blood from both the right coronary artery and the circumflex artery in 10% of the population.
2. The automaticity of the SA node is affected by both the parasympathetic and sympathetic nervous systems. If the SA node fails to generate an impulse, other foci in the atrium, atrioventricular (AV) node, or ventricle can act as “backup” pacemaker sites.

B. AV node. The AV node is located in the anteromedial portion of the right atrium just anterior to the coronary sinus.

1. The impulse generated by the SA node progresses through the atrium to the AV node. The AV node is also innervated by both the parasympathetic and sympathetic nervous systems.
2. The AV node receives its blood supply from the AV node artery, which arises from the posterior descending artery in 80% of the population (Fig. 22.1), from the circumflex artery in 10%, and from both arteries in 10%.
3. Collateral blood supply from the left anterior descending artery makes the AV node somewhat less prone to ischemic damage than the SA node.

C. His bundle and bundle branches

1. After a delay of < 200 milliseconds in the AV node, the electrical impulse is propagated down the His bundle to the right and left bundle branches. The **left bundle branch splits further into anterior and posterior fascicles**. The autonomic nervous system does not have a major effect on conduction below the AV node.
2. The **His bundle and right bundle branch** receive their blood supply from the AV nodal artery and from septal penetrating branches of the left anterior descending artery. The anterior fascicle of the **left bundle branch** receives blood from the septal perforating branches of the left anterior descending

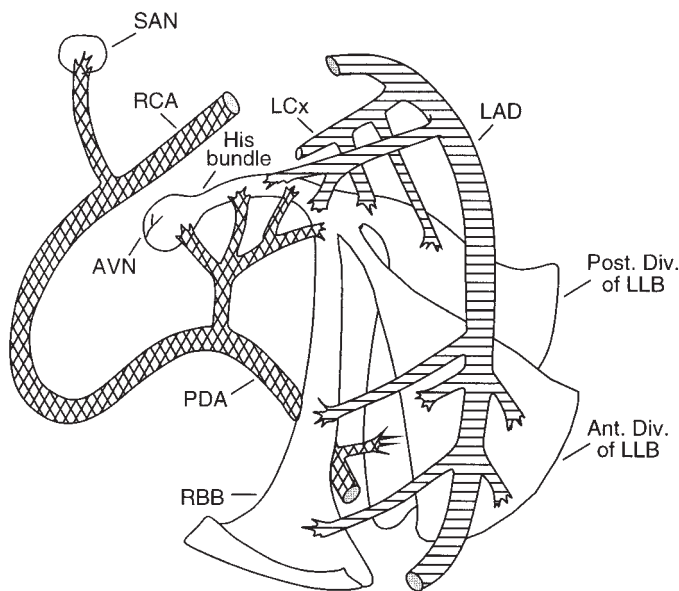


FIGURE 22.1 Diagrammatic representation of the conduction system and its blood supply. SAN, sinoatrial node; RCA, right coronary artery; AVN, atrioventricular node; PDA, patent ductus arteriosus; RBB, right bundle branch; LCx, left circumflex artery; LAD, left anterior descending; LLB, left lateral branch.

artery. The posterior fascicle has a dual blood supply: from the septal perforating branches of the left anterior descending artery and branches of the posterior descending artery.

III. SINUS NODE DYSFUNCTION. Sinus node dysfunction encompasses any dysfunction of the sinus node and includes **inappropriate sinus bradycardia**, **SA exit block**, **SA arrest**, and **tachycardia–bradycardia syndrome**.

A. Clinical presentation. There is a wide range of presentations, and some patients' disease may be asymptomatic.

1. Syncope and **presyncope** are the most dramatic presenting symptoms. **Fatigue**, **angina**, and **shortness of breath** are more subtle consequences of sinus node dysfunction.
2. In the tachycardia–bradycardia syndrome, the primary complaint may be palpitation. Documentation of the arrhythmia may be difficult because of the sporadic and fleeting nature of the problem.

B. Etiology. The intrinsic and extrinsic causes of sinus node dysfunction are listed in Table 22.1. **Idiopathic degenerative disease** is the most common cause of intrinsic sinus node dysfunction, and the incidence increases with age. **Acute coronary syndromes** are a common cause of bradyarrhythmias, occurring in 25% to 30% of patients with myocardial infarction (MI) (Table 22.2).

C. Electrocardiographic findings

1. Inappropriate sinus bradycardia, also known as “chronotropic incompetence,” is defined as a sinus rate of < 60 beats/min that does not increase appropriately

TABLE 22.1 Etiologies of Sinus Node Dysfunction**Intrinsic causes**

Idiopathic degenerative disease
 Coronary artery disease
 Cardiomyopathy
 Hypertension
 Infiltrative disorders (amyloidosis, hemochromatosis, and tumors)
 Collagen vascular disease (scleroderma and systemic lupus erythematosus)
 Inflammatory processes (myocarditis and pericarditis)
 Surgical trauma (valve surgery and transplantation)
 Musculoskeletal disorders (myotonic dystrophy and Friedreich's ataxia)
 Congenital heart disease (postoperative or in the absence of surgical correction)

Extrinsic causes*Drug effects*

β-Blocking agents
 Calcium channel blocking agents
 Digoxin
 Sympatholytic antihypertensives (clonidine, methyldopa, and reserpine)
 Antiarrhythmic drugs
 Type IA (quinidine, procainamide, and disopyramide)
 Type IC (flecainide and propafenone)
 Type III (sotalol and amiodarone)
 Others (lithium, cimetidine, amitriptyline, and phenytoin)

Autonomic influences

Excessive vagal tone
 Carotid sinus syndrome
 Vasovagal syncope
 Well-trained athletes (normal variant and not dysfunction)

Electrolyte abnormalities

Hyperkalemia
 Hypercarbia
 Endocrine disorders—hypothyroidism

*Increased intracranial pressure**Hypothermia**Sepsis*

TABLE 22.2 Incidence of Bradyarrhythmia in the Setting of Acute Myocardial Infarction

Rhythm	Incidence (%)
Sinus bradycardia	25
Junctional escape rhythm	20
Idioventricular escape rhythm	15
First-degree AV block	15
Second-degree, Mobitz type I AV block	12
Second-degree, Mobitz type II AV block	4
Third-degree AV block	15
Right bundle branch block	7
Left bundle branch block	5
Left anterior fascicular block	8
Left posterior fascicular block	0.5

AV, atrioventricular.

with exercise. Inappropriate sinus bradycardia must be differentiated from a low resting heart rate, which may be normal in athletes and sleeping individuals.

2. Sinus arrest, or sinus pause, occurs when the sinus node fails to depolarize on time. Pauses of < 3 seconds may be seen on Holter monitoring in up to 11% of normal adults (especially athletes) and are not a cause for concern. However, **pauses lasting longer than 3 seconds are generally considered abnormal and are suggestive of underlying pathology**, especially if the patient is awake when they occur.
 3. SA exit block, although similar to sinus arrest on the electrocardiographic tracing, may be distinguished by the fact that the **duration of the pause is a multiple of the sinus PP** interval. High-grade SA exit block cannot be differentiated from prolonged sinus arrest and is treated in the same manner.
 4. Tachycardia–bradycardia syndrome, also referred to as “sick sinus syndrome,” is characterized by episodes of sinus or junctional bradycardia interspersed with an atrial tachycardia, usually paroxysmal atrial fibrillation.
- D. Diagnostic testing.** Invasive testing is used when noninvasive methods have failed to yield a diagnosis and sinus node dysfunction is still strongly suspected.
1. **Noninvasive testing**
 - a. **Electrocardiogram (ECG).** In evaluating sinus node dysfunction, the initial workup should include a 12-lead ECG, followed by a 24-hour to 48-hour ambulatory ECG monitoring, if necessary. Use of a diary during the recording period can help correlate symptoms with the cardiac rhythm. For less frequent events, a loop recorder or an event recorder may be used to assess symptoms over a 2-week to 4-week period. Stress testing can help document the severity of chronotropic incompetence.
 - b. Autonomic testing includes physical maneuvers, such as carotid sinus massage and tilt table testing, as well as pharmacologic interventions to test the autonomic reflexes.
 - (1) Carotid sinus massage distinguishes intrinsic sinus pause/sinus arrest from a pause due to **carotid sinus hypersensitivity**, which is a 3-second

or longer pause and/or a ≥ 50 mm Hg or greater drop in blood pressure that occurs with massage of the carotid sinus (firm pressure applied to one carotid sinus at a time for 5 seconds). **Carotid sinus massage should not normally precipitate sinus pause/sinus arrest**, although it will decrease the rate of depolarization of the SA node and slow conduction in the AV node.

- (2) Tilt table testing may help differentiate between syncope caused by sinus node dysfunction and that due to autonomic dysfunction. **Bradycardic episodes precipitated by tilt table testing are usually caused by autonomic dysfunction and not by sinus node dysfunction.**
- (3) Pharmacologic testing may be used to differentiate between sinus node dysfunction and autonomic dysfunction. Total autonomic blockade is achieved after administration of atropine 0.04 mg/kg and propranolol 0.2 mg/kg. The resulting intrinsic heart rate represents the sinus node rate, devoid of autonomic influences. Assuming that the normal intrinsic heart rate (in beats/min) is defined by the formula

$$\text{Intrinsic heart rate} = 118.1 - (0.57 \times \text{age})$$

then an intrinsic heart rate lower than predicted using this formula is consistent with sinus node dysfunction; an intrinsic heart rate close to the predicted rate in a patient with a clinical presentation of sinus node dysfunction is suggestive of an autonomic dysfunction as a cause of the bradyarrhythmia.

2. **Invasive testing.** The two most common tests use indirect measurements of SA node function. Direct measurement of SA node function is laborious and rarely performed.

- a. Sinus node recovery time (SNRT) is the time it takes the SA node to recover following paced overdrive suppression of the node.

- (1) **A delay of longer than 1,400 milliseconds is considered abnormal.** This measurement may be corrected by subtracting the intrinsic sinus cycle length (in milliseconds) from the recovery time. **A corrected SNRT > 550 milliseconds is suggestive of sinus node dysfunction.**

- (2) The limitations of this test are as follows:

- (a) It is an indirect measurement of SA node function and reflects both sinoatrial node conduction time (SACT) and automaticity.
 - (b) It may be falsely shortened by an SA node entrance block during atrial pacing (due to failure of the paced impulse to reset the sinus node) or falsely prolonged by an SA node exit block (the sinus node is normal but the impulse cannot leave the node), which affects its specificity.
 - (c) The SNRT is not prolonged in all patients with sinus node dysfunction, which affects its sensitivity.

- b. Sinoatrial node conduction time

- (1) The steady-state atrial rate is determined (A_1 – A_1 interval or the time between P waves). Then premature atrial **extra stimuli** (A_2) are introduced by pacing high in the right atrium, starting in late diastole at progressively shorter intervals until atrial refractoriness is found (i.e., A_2 does not result in a P wave). The duration before the next spontaneous atrial impulse (A_3) is measured and the baseline rate is subtracted.

$$\text{SACT} = (A_2 - A_3 \text{ interval}) - (A_1 - A_1 \text{ interval})$$

- (2) The test assumes that SA node automaticity is not affected by pacing, that conduction time into the node is equal to conduction time out of the node, and that there is no shift in the principal pacemaker site.

- E. **Therapy.** Treatment for symptomatic sinus node dysfunction may be pharmacologic, pacing, or a combination of both.

1. Indications for pacing in sinus node dysfunction are determined by symptoms (e.g., correlation with a documented arrhythmia; Table 22.3). Another common indication is when drug therapy that causes sinus node dysfunction cannot be stopped or changed.
2. Medications that suppress sinus node automaticity should be stopped if possible. If this is not possible, it may be necessary to place a temporary or permanent pacemaker (Table 22.3).
3. For patients with **tachycardia–bradycardia syndrome**, a pacemaker is often placed for management of the bradyarrhythmia, and antiarrhythmic drugs are added for treatment of the tachycardia episodes.
4. Acute treatment for patients with **symptomatic sinus node dysfunction** includes the following:
 - (a) Atropine (0.04 mg/kg intravenous bolus)
 - (b) Temporary pacing for patients whose conditions fail to respond to drug therapy
 - (c) Isoproterenol (starting at 1 µg/min intravenously), which may be used as a bridge to pacemaker placement. Isoproterenol is not indicated in most patients with cardiac arrest

IV. AV CONDUCTION DISTURBANCES. These disturbances are classified as first-degree, second-degree, or third-degree block, depending on the severity of the conduction abnormality.

A. Classification

1. First-degree AV block is characterized by the prolongation of the PR interval beyond 200 milliseconds. This finding may occur as a normal variant in 0.5% of asymptomatic young adults without overt heart disease. In older individuals, it is most often caused by idiopathic degenerative disease of the conducting system.
2. **Second-degree AV block**
 - a. Second-degree AV block is characterized by **a failure of one or more, but not all, atrial impulses to conduct to the ventricles**. The block may be at any level of the AV conduction system.
 - b. When more than one atrial impulse is present for each ventricular complex, the rhythm may be described as a ratio of the number of atrial impulses to the number of ventricular complexes (for three P waves preceding each QRS complex, 3:1 second-degree AV block is present).
 - (1) Lesser degrees of AV block (i.e., 4:3 or 3:2) with a prolonging PR interval prior to a nonconducted atrial impulse are described as **Mobitz type I AV block** (also known as Wenckebach block).
 - (a) The conducted impulse of a **Mobitz type I block** will generally be narrow, and the site of block is often in the AV node above the His bundle.
 - (b) A Mobitz type I block with a bundle branch block is still likely to be above the His bundle, but a His bundle ECG is needed to confirm the level of block.
 - (2) High-grade AV block (3:1, 4:1, or greater) is typically described as **Mobitz type II AV block**. The conducted impulses will generally be preceded by constant PR intervals and have a wide QRS morphology (right bundle branch block [RBBB] or left bundle branch block [LBBB] pattern). The site of block is often below the AV node. A **Mobitz type II block** is usually intra-Hisian or infra-Hisian and has a greater propensity for progressing to third-degree AV block.
 - (3) Pure 2:1 conduction patterns cannot be reliably classified as Mobitz type I or type II, and if diagnostic maneuvers (such as exercise) are not able to elucidate one type of second-degree block versus the other, an electrophysiology study may be warranted.

TABLE 22.3 Indications for Permanent Pacing

Indication	Class I	Class II	Class III
SND	<ol style="list-style-type: none"> 1. SND documented in association with symptomatic bradycardia and due to factors that are irreversible or due to essential drug therapy 2. Symptomatic chronotropic incompetence 	<ol style="list-style-type: none"> Ila. No clear association between SND with heart rate < 40 beats/min and symptoms can be documented Ilb. In minimally symptomatic patients, chronic heart rate < 40 beats/min while awake 	<ol style="list-style-type: none"> 1. SND with marked sinus bradycardia or pauses but no associated symptoms including that due to long-term drug therapy 2. SND in patients with symptoms suggestive of bradycardia that are clearly documented as <i>not</i> associated with a slow heart rate 3. SND with symptomatic bradycardia due to nonessential drug therapy
Acquired AV block	<ol style="list-style-type: none"> 1. Third-degree AV block at any anatomic level, associated with any one of the following conditions: <ol style="list-style-type: none"> a. Bradycardia with symptoms presumed to be due to AV block b. Arrhythmias and other medical conditions that require drugs that result in symptomatic bradycardia c. Documented periods of asystole ≥ 3.0 s, or an escape rhythm below the AV node, or any escape rate < 40 beats/min in awake, symptom-free individuals in sinus rhythm d. Documented pauses > 5 s in awake, symptom-free patients who are in atrial fibrillation 	<ol style="list-style-type: none"> Ila. 1. Asymptomatic third-degree AV block at any anatomic site with average awake ventricular rates ≥ 40 beats/min 2. Asymptomatic type II second-degree AV block. Of note, when type II second-degree AV block occurs with a wide QRS, including isolated right bundle branch block, pacing becomes a class I recommendation 3. Asymptomatic type I second-degree AV block at intra-His or infra-His levels found incidentally at EP study performed for other indications 	<ol style="list-style-type: none"> 1. Asymptomatic one-degree AV block 2. Asymptomatic type I second-degree AV block at the supra-His (AV node) level or not known to be intra-Hisian or infra-Hisian 3. AV block expected to resolve and unlikely to recur (e.g., drug toxicity and Lyme disease)

Indication	Class I	Class II	Class III
	<p>e. After catheter ablation of the AV junction</p> <p>f. Postoperative AV block that is not expected to resolve</p> <p>g. Neuromuscular diseases with AV block such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb's dystrophy (limb girdle), and peroneal muscular dystrophy</p> <p>h. Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 beats/min or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node.</p> <p>i. Permanent pacemaker implantation is indicated for second-degree or third-degree AV block during exercise in the absence of myocardial ischemia</p> <p>2. Second-degree AV block regardless of type or site of block, with associated symptomatic bradycardia</p>	<p>4. First-degree AV block with symptoms suggestive of pacemaker syndrome and documented alleviation of symptoms with temporary AV pacing</p>	
Post-myocardial infarction	<p>1. Persistent second-degree AV block in the His-Purkinje system with bilateral bundle branch block or third-degree AV block within or below the His-Purkinje system after acute myocardial infarction</p>	<p>Ila. None</p> <p>Ilb.</p> <p>1. Persistent second-degree or third-degree AV block at the AV node level, even in the absence of symptoms</p>	<p>1. Transient AV block without intraventricular conduction defect</p> <p>2. Transient AV block in the presence of isolated left anterior fascicular block</p>

(Continued)

Indication	Class I	Class II	Class III
	2. Transient advanced (second-degree or third-degree) infranodal AV block and associated bundle branch block. If the site of block is uncertain, an EP study may be necessary 3. Persistent and symptomatic second-degree or third-degree AV block		3. Acquired left anterior fascicular block in the absence of AV block 4. Persistent first-degree AV block in the presence of bundle branch block that is old or age indeterminate
Chronic bifascicular and trifascicular blocks	1. Intermittent third-degree AV block 2. Type II second-degree AV block 3. Alternating bundle branch block	IIa. 1. Syncope not proved to be due to AV block when other likely causes have been excluded, specifically ventricular tachycardia 2. HV interval > 100 milliseconds 3. Pacing-induced block below the His that is not physiologic	1. Fascicular block without AV block or symptoms 2. Fascicular block with first-degree AV block without symptoms
Carotid sinus hypersensitivity (carotid sinus irritability) and neurally mediated syncope	1. Recurrent syncope caused by carotid sinus stimulation; minimal carotid sinus pressure induces ventricular asystole of > 3 s duration in the absence of any medication that depresses the sinus node or AV conduction	IIb. None IIa. 1. Recurrent syncope without clear, provocative events and with a hypersensitive cardioinhibitory response 2. Syncope of unexplained origin when major abnormalities of sinus node function or AV conduction are discovered or provoked in EP studies	1. A hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms 2. A hyperactive cardioinhibitory response to carotid sinus stimulation in the absence of symptoms A hyperactive cardioinhibitory response to carotid sinus stimulation in the presence of vague symptoms such as dizziness, light-headedness, or both

Indication	Class I	Class II	Class III
		IIb. 1. Neurally mediated syncope with significant bradycardia reproduced by a head-up tilt with or without isoproterenol and other provocative maneuvers	3. Recurrent syncope, light-headedness, or dizziness in the absence of a hyperactive cardioinhibitory response 4. Situational vasovagal syncope in which avoidance behavior is effective

Class I: conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective.

Class II: conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of pacing.

Class IIa: weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: usefulness/efficacy is less well established by evidence/opinion.

Class III: conditions for which there is evidence and/or general agreement that pacing is not useful/effective and in some cases may be harmful.

SND, sinus node dysfunction; AV, atrioventricular; LV, left ventricular; EP, electrophysiologic; HV, half-value.

Adapted from Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to revise the ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices). *J Am Coll Cardiol*. 2008; 51:2085-2105.

3. Third-degree AV block, or **complete heart block**, may be acquired or congenital.
 - a. Of patients with **congenital complete heart block**, 60% are female. Of children with congenital complete heart block, 30% to 50% of their mothers have connective tissue disease, usually systemic lupus erythematosus.
 - b. Acquired AV block occurs most frequently in the seventh decade and more commonly affects males.
- B. Clinical presentation**
1. **Signs and symptoms**
 - a. First-degree AV block is generally not a cause of symptoms.
 - b. Second-degree AV block sometimes results in symptoms; however, high-grade second-degree AV block may progress to third-degree AV block, which can frequently cause symptoms.
 - c. Depending on the ventricular escape rate, patients with **third-degree AV block** may experience **fatigue** or **syncope**.
 2. **Physical findings.** The amplitude of the arterial pulse and venous waveform varies, depending on the timing of atrial filling of the ventricles.
 - a. Second-degree AV block is associated with a periodic change in amplitude. In patients with **third-degree AV block**, amplitude is constantly changing, for example, periodic appearance of cannon *a* waves (large-amplitude waves in the venous pulsations seen in the neck when the atria contracts against a closed tricuspid valve).
 - b. Heart sounds are similarly affected by the change in filling duration of the ventricles.
 - (1) **The first heart sound (S_1)** becomes softer as the PR interval is prolonged, resulting in a soft S_1 in first-degree AV block, a progressive softening of S_1 in type I second-degree AV block, and a constantly changing S_1 in third-degree AV block.
 - (2) Third-degree AV block may also result in a functional systolic ejection murmur.
- C. Etiology.** The causes of AV block are listed in Table 22.4; the most common cause is **idiopathic fibrosis**. **Acute MI** results in AV block in 14% of patients with inferior infarction and 2% of those with anterior infarction, usually within the first 24 hours.
- D. Diagnostic testing**
1. **First-degree AV block.** Measuring a PR interval longer than 200 milliseconds in adults and 180 milliseconds in children makes up the diagnosis. A P wave precedes each QRS, and both the P and the QRS are morphologically normal.
 2. **Second-degree AV block**
 - a. The diagnosis of **Mobitz type I** is made when the following criteria are met on the ECG:
 - (1) Sequential and gradual prolongation of the PR interval terminated by a nonconducted P wave
 - (2) Prolongation of the PR interval occurring in progressively shorter increments in “typical” Wenckebach, which results in progressive shortening of the RR intervals prior to the nonconducted atrial impulse
 - (3) Duration of the pause following the nonconducted P wave is less than the sum of any two consecutively conducted beats
 - (4) Decreased PR interval following the pause when compared with the pre-pause PR interval
 - (5) “Grouped beating,” a pattern of repeated groups of QRS complexes characteristic of Wenckebach block
 - b. Mobitz type II second-degree AV block is less common than type I.
 - (1) The PR interval is constant with a sudden nonconducted P wave (Fig. 22.2), in contrast to nonconducted premature atrial contractions that have a varying PR interval.

TABLE 22.4 Causes of Atrioventricular Block

Drug effects
Digoxin
β -Blockers
Certain calcium channel blockers (nondihydropyridines)
Membrane-active antiarrhythmic drugs
Ischemic heart disease
Acute myocardial infarction
Chronic coronary artery disease
Idiopathic fibrosis of the conduction system
Lenegre's disease
Lev's disease
Congenital heart disease
Congenital complete heart block
Ostium primum atrial septal defect
Transposition of the great vessels
Maternal systemic lupus erythematosus
Calcific valvular disease
Cardiomyopathy
Infiltrative disease
Amyloidosis
Sarcoidosis
Hemochromatosis
Infectious/inflammatory diseases
Endocarditis
Myocarditis (Chagas disease, Lyme disease, rheumatic fever, tuberculosis, measles, and mumps)
Collagen vascular diseases (scleroderma, rheumatoid arthritis, Reiter's syndrome, systemic lupus erythematosus, ankylosing spondylitis, and polymyositis)
Metabolic
Hyperkalemia
Hypermagnesemia
Endocrine—Addison's disease
Trauma
Cardiac surgery
Radiation
Catheter trauma
Catheter ablation
Tumors
Mesothelioma
Hodgkin's disease
Malignant melanoma
Rhabdomyosarcoma
Neurally mediated
Carotid sinus syndrome
Vasovagal syncope
Neuromyopathic disorders
Myotonic muscular dystrophy
Slowly progressive X-linked muscular dystrophy



FIGURE 22.2 Mobitz type II second-degree atrioventricular block with 3:1 conduction.

- (2) Each QRS complex may have multiple P waves, which are designated by the number of P waves before each conducted QRS (3:1, 4:1, etc.). The QRS complex is typically not narrow (a narrow QRS complex is suggestive of a Mobitz type I block).
3. **Third-degree AV block** (Fig. 22.3)
 - a. Third-degree AV block is characterized by the identification of **complete dissociation of the atrial and ventricular electrical activities** (no temporal relationship exists between the P waves and the QRS complexes), with atrial activity more rapid than ventricular activity. Using calipers, it is possible to march out the progression of the P waves to determine the atrial rate.
 - b. Third-degree AV block is only one cause of AV dissociation; **not all AV dissociation is third-degree AV block**. For example, conditions where the ventricles are depolarizing faster than the atria—such as accelerated junctional rhythm or ventricular tachycardia—also result in AV dissociation if there is a lack of retrograde conduction over the AV node.
- E. **Therapy.** Patients with first-degree AV block and Mobitz type I AV block usually do not require therapy. Permanent pacing is indicated for Mobitz type II AV block and third-degree AV block. (See Table 22.3 for complete indications for pacing.)
 1. Medical therapy may be used as a bridge to pacing but it has no role in long-term treatment.
 - a. The principal drug used as a bridge to pacing is **atropine**,
 - (1) which reduces heart block due to hypervagotonia but not due to AV nodal ischemia;
 - (2) which is more useful for AV block in inferior MI than anterior MI;
 - (3) which does not increase infranodal conduction (will not improve second-degree or third-degree AV block that is below the AV node);
 - (4) which is ineffective in the denervated hearts of transplant patients;
 - (5) which is used with caution (if at all) in Mobitz type II AV block due to a possible paradoxical decrease in heart rate (as atrial rate increases, AV conduction decreases, and a 2:1 block with an atrial rate of 80 beats/min and a ventricular rate of 40 beats/min may be converted to a 3:1 block with an atrial rate of 90 beats/min and a ventricular rate of 30 beats/min).
 - b. Digoxin-specific Fab fragments may be used to treat patients with symptomatic AV blocks related to the use of digitalis. The number of vials = $\text{weight (kg)} \times \text{digoxin serum concentration (ng/mL)} / 100$.
 2. **Pacing**
 - a. Third-degree AV block as a complication of inferior MI is usually temporary and thus usually only requires **temporary pacing**.
 - b. However, complete heart block as a result of anterior MI often requires **permanent pacing** (Table 22.3).
 - c. Acquired third-degree AV block usually requires pacing, but patients with congenital third-degree AV block often have a sufficiently rapid escape rhythm to prevent symptoms and avoid permanent pacemaker implantation.

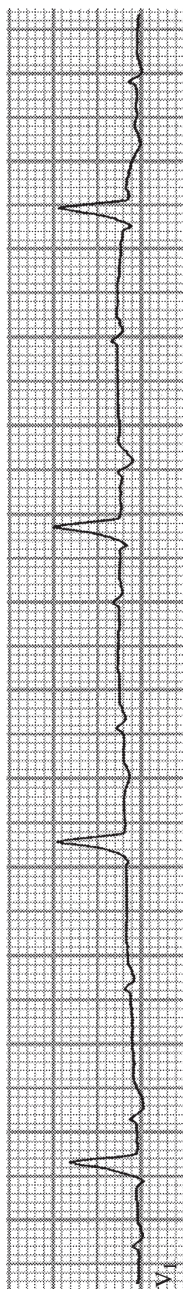


FIGURE 22.3 Third-degree atrioventricular block with sinus tachycardia and right bundle branch block.

V. JUNCTIONAL RHYTHMS. Junctional rhythms arise from the area surrounding the AV node, including the approaches to the node, the node itself, and the bundle of His. This area has an intrinsic rate of 30 to 60 beats/min and serves as an escape mechanism to prevent ventricular asystole in case of complete AV block. Junctional rhythm that is faster than the sinus rhythm is referred to as **accelerated junctional rhythm**.

A. Clinical presentation. Patients usually do not develop symptoms that are directly attributable to accelerated junctional rhythm. The **physical findings of AV dissociation may be noted** and are the same as those seen in third-degree AV block.

B. Etiology

1. Accelerated junctional rhythm is seen in approximately **10% of patients with acute MI**. More than one-half of these patients have inferior MI and about one-third have anterior infarctions.
2. Digitalis toxicity by itself does not seem to cause accelerated junctional rhythm, as evidenced in persons with normal hearts who take accidental overdoses of digoxin. **Concomitant heart disease** is required to develop accelerated junctional rhythm.
3. Other causes of accelerated junctional rhythm are valve surgery, acute rheumatic fever, direct current cardioversion, cardiac catheterization, serious infection, chronic obstructive pulmonary disease, systemic amyloidosis, and uremia with hyperkalemia.

C. ECG findings

1. Accelerated junctional rhythm

- a. **Unless the junctional rhythm causes retrograde activation of the atria**, the P wave is normal in morphologic characteristics. The QRS complex has a normal duration, unless there is concomitant bundle branch block. The distinguishing characteristic of accelerated junctional rhythm is the AV dissociation and changing PR interval (Fig. 22.4).
 - b. **The difference between accelerated junctional rhythm and third-degree AV block is the fact that the ventricular rate is faster than the atrial rate in accelerated junctional rhythm and slower than the atrial rate in third-degree AV block.**
2. **Junctional rhythm.** In the absence of a sinus beat, the AV node can act as a backup pacemaker. The ECG findings are an absence of P waves (or retrograde P waves immediately before or after the QRS complex), a narrow QRS complex, and a rate of 30 to 60 beats/min.

D. Therapy

1. Therapy for junctional rhythm secondary to SA node failure or AV block is as previously outlined for AV conduction disturbances.
2. Patients with accelerated junctional rhythm do not usually require therapy for the arrhythmia, although management of the underlying cause is indicated.
3. Suppression of accelerated junctional rhythm may be achieved by **increasing the atrial rate with drugs** (e.g., atropine and adrenergics) or **pacing**.
4. Digoxin-induced accelerated junctional rhythm is an indication to stop digoxin but it does not usually require administration of digoxin-specific Fab fragments.

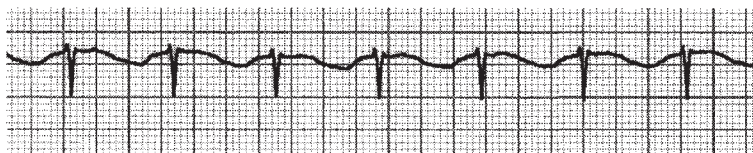


FIGURE 22.4 Accelerated junctional rhythm.

VI. INTRAVENTRICULAR CONDUCTION DISTURBANCES. Conduction disturbances due to blockage below the AV node are classified on the basis of the intraventricular conduction system. An intraventricular conduction disturbance (IVCD) does not itself cause bradyarrhythmia, but it may be associated with any of the other rhythms that cause bradycardia. When associated with an acute MI, an IVCD predicts a worse outcome.

A. Etiology

1. The causes of IVCDs are similar to those that cause AV block (Table 22.4); **idiopathic degenerative conduction disease** and **acute ischemic syndromes** are the most common causes.
2. IVCDs increase with age and affect up to 2% of individuals older than 60 years.
3. The incidence of IVCDs is increased in persons with structural heart disease, especially those with coronary artery disease.

B. ECG findings

1. The ECG findings of IVCDs are summarized in Table 22.5 and examples are presented in Figures 22.5 to 22.8. As shown, **IVCDs may be further classified by the number of fascicles they affect.**
2. **Fascicular blocks**
 - a. Unifascicular blocks affect only one of the three fascicles. Examples are RBBB, left anterior fascicular block, and left posterior fascicular block (LPFB).
 - b. Bifascicular block is present when conduction disturbances affect two of the fascicles, most commonly the right bundle branch and the left anterior fascicle. Approximately, 6% of these patients progress to complete heart block. RBBB with LPFB is less common, but the progression to complete heart block is more common.
 - c. “Trifascicular block” is said to be present when there is a combination of bifascicular block and first-degree AV block (Fig. 22.8).

C. Therapy. Pacing is indicated in patients with bifascicular block who have intermittent symptomatic complete heart block and in patients with bifascicular or trifascicular block with asymptomatic intermittent Mobitz type II AV block (Table 22.3).

TABLE 22.5 **Electrocardiographic Features for the Fascicular and Bifascicular Blocks**

ECG finding	LBBB	LAFB	LPFB	RBBB	RBBB and LAFB	RBBB and LPFB
QRS axis		$\geq -45^\circ$	$+90^\circ$ to $+120^\circ$		-60° to -120°	$\geq +120^\circ$
QRS duration	≥ 120 milliseconds	Normal	Normal	≥ 120 milliseconds	≥ 120 milliseconds	≥ 120 milliseconds
Leads I/aVL	broad monophasic R	qR	rS	qRS with wide terminal S	qR	rS
Leads II, III, and aVF		rS	qR		rS	qR
Leads V_1 and V_2	rS or QS			rsR' or rSR'	rsR' or rSR'	rsR' or rSR'
Leads V_5 and V_6		S	no Q's	qRS		

ECG, electrocardiogram; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block.

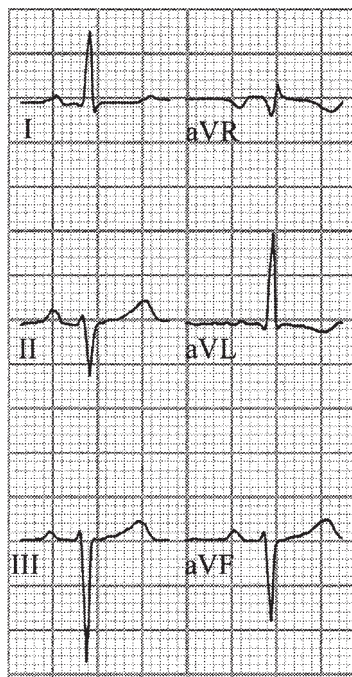


FIGURE 22.5 Left anterior hemiblock.

VII. POSTSURGICAL BRADYARRHYTHMIAS

A. Etiology. Bradyarrhythmias following cardiac surgery are common.

1. Valvular surgery and septal myectomy can cause mechanical damage to the conduction system, leading to AV blocks and IVCDs. For example, there is an approximately 7% incidence of postoperative permanent pacemaker implantation for high-grade AV block after conventional aortic valve replacement in patients with severe calcific aortic stenosis (this may be partly due to a higher prevalence of infranodal conduction system disease at baseline). Also, there is a high incidence of LBBB after septal myectomy, due to the presence of the left bundle branch in the myocardium being excised.
2. Prolonged ischemic time during cardiac transplantation can lead to sinus node damage.

B. Therapy. Because postsurgical bradyarrhythmias may be only temporary, the decision to proceed to **permanent pacing** should be made after 5 to 7 days. The same criteria listed in Table 22.3 are used to determine the need for a pacemaker. Permanent pacing is required in 2% to 3% of patients following valve surgery (when considering all types) and in upward of 10% of transplant patients.

VIII. PULSELESS ELECTRICAL ACTIVITY. Pulseless electrical activity is defined as the absence of a pulse or blood pressure measured by usual methods, with the continued presence of electrical activity of the heart.

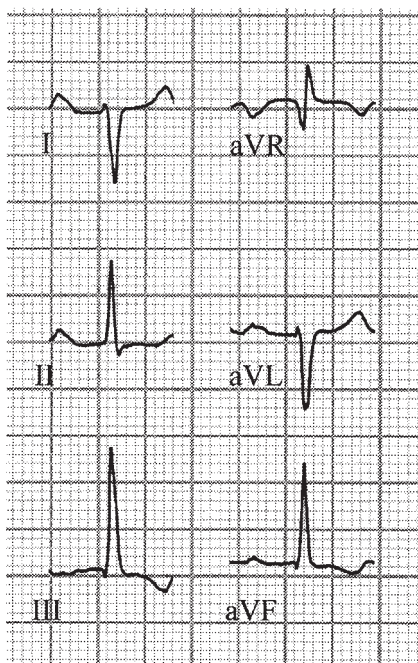


FIGURE 22.6 Left posterior hemiblock.

A. Etiology

1. Pulseless electrical activity may result from a variety of **rhythm disturbances**, such as electrical–mechanical dissociation, idioventricular rhythms, and ventricular tachycardias. When the electrical activity is organized and within the physiologic range, the term **electrical–mechanical dissociation** is used.
2. A variety of clinical situations are also associated with pulseless electrical activity, a potentially manageable condition if certain actions are undertaken rapidly (Table 22.6).

B. Therapy

1. Specific management of the underlying cause is most likely to result in a successful outcome (Table 22.6).
2. Emergency intervention should be initiated at once, including the following:
 - (a) Effective cardiopulmonary resuscitation (CPR) and airway management
 - (b) Epinephrine, 1 mg intravenous push every 3 to 5 minutes
 - (c) A one-time intravenous push of 40 IU of vasopressin may be considered as an alternative to epinephrine during the first or second round of advanced cardiac life support
 - (d) Atropine is no longer recommended for routine administration during advanced cardiac life support for pulseless electrical activity, as per 2010 ACC/AHA guidelines.
 - (e) Discovery and correction of the underlying reason for the pulseless electrical activity (see Table 22.6) remains the paramount concern along with performing

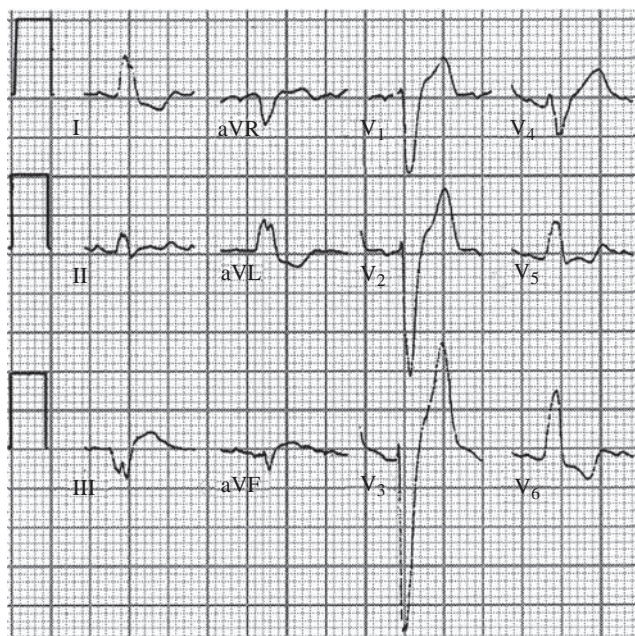


FIGURE 22.7 Left bundle branch block.

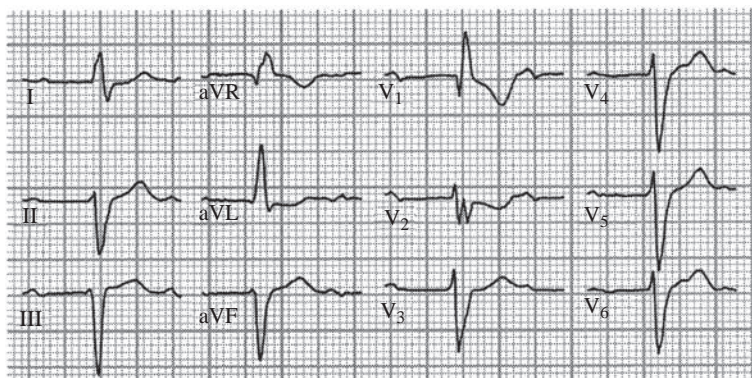


FIGURE 22.8 First-degree atrioventricular block with right bundle branch block and left anterior hemiblock.

effective CPR. The “H’s and T’s” of hypoxia, hypovolemia, hypothermia, hyperkalemia, acidosis (“hyper-H+”), tension pneumothorax, thrombosis (coronary or pulmonary), tamponade, and toxins must be considered and addressed as soon as possible.

TABLE 22.6 Conditions That Cause Pulseless Electrical Activity

Condition	Clues	Management
Hypovolemia	History and flat neck veins	Volume infusion
Hypoxia	Cyanosis, blood gases, and airway problems	Ventilation
Cardiac tamponade	History (trauma, renal failure, and malignancy), no pulse with CPR, vein distention; impending tamponade—tachycardia, hypotension, and low pulse pressure	Pericardiocentesis
Tension pneumothorax	History (asthma, ventilator, chronic obstructive pulmonary disease, and trauma), no pulse with CPR, neck vein distention, and tracheal deviation	Needle decompression
Hypothermia	History of exposure to cold, central body temperature, and ECG	Gradual warming
Massive pulmonary embolism	History and no pulse felt with CPR	Pulmonary arteriogram, surgical embolectomy, and thrombolytics
Drug overdose (tricyclics, digoxin, β -blockers, and calcium channel blockers)	Bradycardia, history of ingestion, empty bottles at the scene, pupils, and neurologic examination	Drug screens, intubation, lavage, activated charcoal, and lactulose per local protocols
Hyperkalemia	History of renal failure, diabetes, recent dialysis, medications, and ECG	Calcium chloride (immediate); then combination of insulin, glucose, and sodium bicarbonate; then sodium polystyrene sulfonate/sorbitol; and dialysis (long term)
Preexisting acidosis	Renal failure	Sodium bicarbonate and hyperventilation
Acute massive MI	History, ECG and enzymes	Treatment for cardiogenic shock

CPR, cardiopulmonary resuscitation; ECG, electrocardiogram; MI, myocardial infarction.

IX. ASYSTOLE

A. Clinical presentation. Asystole is defined as the absence of myocardial electrical activity. *It should be confirmed by switching between several leads or changing the position of the defibrillation paddles.*

- Most patients with asystole present in a code situation. Persons outside of the hospital who are found to have asystole by the initial responding team usually have it as a result of **profound myocardial ischemia**. The possibility of a successful outcome in this situation is extremely small.

2. Hospital inpatients monitored by telemetry, on the other hand, may have a favorable outcome.
 - B. Etiology.** Asystole may be due to profound parasympathetic suppression of both atrial and ventricular activities, stunning of the myocardium due to electrical defibrillation, complete heart block, or prolonged myocardial ischemia. Also, many of the causes of pulseless electrical activity may also lead to asystole, and the same search for obvious and immediately reversible causes is warranted (Table 22.6).
 - C. Therapy.** Management consists of effective **CPR, airway protection**, and a **similar management algorithm** to pulseless electrical activity.
 1. Routine shocking is strongly discouraged. Electrical shocks have not been demonstrated to have any benefit in the management of asystole and may in fact produce a stunned myocardium, leading to a delay in the return of a rhythm.
 2. Pacing for asystole is controversial. If pacing is to have any effect, it must be initiated early. Patients with asystole due to myocardial ischemia are unlikely to respond to pacing, but those with asystole due to other causes might respond.
 3. As with the 2010 revised guidelines for management of pulseless electrical activity, atropine is no longer recommended for routine use in the resuscitation of the asystolic patient.
- X. CAROTID SINUS HYPERSENSITIVITY.** Carotid sinus hypersensitivity, defined as a sinus pause of 3 seconds or more and/or a drop in blood pressure of 50 mm Hg or more with carotid sinus massage, is common, affecting up to one-third of older men with coronary artery disease. Carotid sinus hypersensitivity may be purely cardioinhibitory, purely vasodepressive, or a combination of both. **Carotid sinus syndrome** is present when carotid sinus hypersensitivity is accompanied by syncope or near syncope.
- A. Etiology and pathophysiology**
1. The **cause of carotid sinus hypersensitivity and carotid sinus syndrome is unknown**. It is more common in older individuals, particularly those with atherosclerotic disease. Carotid sinus syndrome may be precipitated by the patient stretching his or her neck (such as with shaving or turning the head) or wearing a tight collar, but often a precipitating event cannot be found.
 2. Sites of potential lesions causing carotid sinus hypersensitivity are the sternocleidomastoid muscle, the central nervous system, and the feedback loops between the cardiovascular and the central nervous systems.
 3. It has been demonstrated that the **carotid sinus function is intact** and the sinus is not hypersensitive in the true sense. Some investigators have suggested that carotid sinus syndrome be renamed carotid sinus irritability to better reflect its pathophysiology.
- B. Diagnostic testing.** A patient with suspected carotid sinus hypersensitivity/carotid sinus syndrome should be tested lying down with ECG and blood pressure monitoring.
1. Carotid sinus massage is performed by placing firm manual pressure over the carotid sinus located at the bifurcation of the carotid artery for not more than 5 seconds. Only one sinus at a time is compressed, and the temporal artery should be lightly palpated to ensure that complete occlusion of the artery does not occur.
 2. Potential risks of carotid sinus massage are transient ischemic attack and stroke. This test should not be performed if a carotid bruit is present. Tilting the patient to an upright position will increase the diagnostic yield of the test but it may also result in false-positive outcomes.
- C. Therapy**
1. Carotid sinus hypersensitivity by itself generally does not require treatment. However, therapy is warranted if carotid sinus hypersensitivity is demonstrated to be the cause of syncope or near syncope.

2. For purely cardioinhibitory or the mixed type of carotid sinus syndrome, the therapy of choice is pacing (Table 22.3).
3. Management of vasodepressive carotid sinus syndrome is more difficult, and pacing is generally ineffective.

ACKNOWLEDGMENTS: *The author thanks Drs. Christopher Cole, Gregory Bashian, and Oussama Wazni for their significant contributions to earlier editions of this chapter.*

LANDMARK ARTICLES

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CHAPTER

23

Edmond M. Cronin

Sudden Cardiac Death

- I. DEFINITION AND EPIDEMIOLOGY.** Sudden cardiac death (SCD) is defined as death following cardiac arrest in a patient with or without known preexisting heart disease in whom the mode and time of death are unexpected (1). The generally accepted time-frame between the onset of symptoms and loss of consciousness is 1 hour, although some patients who receive medical interventions may live for much longer after the initiating event before expiring. If the patient survives the event, due to defibrillation or spontaneous recovery, it is labeled sudden cardiac arrest (SCA). The incidence of SCD in the United States is estimated at 460,000 cases per annum, accounting for 10% to 15% of all deaths from natural causes and about 50% of all cardiac deaths. SCD exhibits a bimodal age distribution with peaks between birth and 6 months of age and then rises steadily from age 30. A male preponderance is observed in all age groups, narrowing after age 65, and is attributable to an increased incidence of coronary artery disease (CAD). While the absolute risk of SCD is greater among high-risk populations, most SCDs occur in patients who have not been identified as being at risk, being the first presentation of cardiovascular disease in approximately 25% of patients.

It is likely that ventricular fibrillation (VF) or ventricular tachycardia (VT) is the initiating rhythm in most cases of SCA. As the time from onset and rhythm identification increases, the proportion of VF decreases. This suggests that asystole and pulseless electrical activity (PEA) are frequently the result of prolonged VF and resultant ischemia and hypoxia. However, a significant proportion of SCA is due to bradyarrhythmias and pump failure. The proportion of these deaths is slightly higher in patients with advanced heart failure, although tachyarrhythmias still predominate.

II. CAUSES OF SCD

A. Coronary artery disease accounts for 80% or more of episodes of SCD in Western societies, and SCD is the first presentation of CAD in 20% to 25% of patients. However, the extent to which acute ischemia plays a role in initiating a trigger for SCD is unclear. Autopsy data have demonstrated a recent occlusive thrombus in only about 15% to 20% of patients, while evidence of a remote infarct is identified in 40% to 70% of cases. The majority (80%) of SCD episodes in patients with CAD are considered to be primary (i.e., no precipitating factor can be identified), whereas secondary causes like myocardial ischemia/infarction, drug toxicity or proarrhythmia, decompensated heart failure, or electrolyte imbalance can be identified in the minority. Patients with reduced left ventricular ejection fraction (LVEF) and frequent premature ventricular contractions (PVCs) are identified as a particularly high-risk subgroup. A study of patients implanted with a loop recorder with recent myocardial infarction (MI) and ejection fraction (EF) $\leq 40\%$ found that the terminal rhythm was VF in 86% of sudden deaths, and 50% of all deaths, with bradyarrhythmias in the remaining 50%.

B. Cardiomyopathies

- 1. Dilated cardiomyopathy (DCM).** Patients with DCM represent the second largest group of patients who experience SCD, accounting for approximately 10% of cases. The annual mortality from DCM is 11% to 15%, with SCD accounting for about 30% of all deaths in this population. The presence of reduced LVEF and syncope are markers of a high risk of SCD in these patients. There is also a higher incidence of sudden deaths related to bradyarrhythmias and PEA in patients with advanced disease.
- 2. Hypertrophic cardiomyopathy (HCM).** The incidence of SCD in patients with HCM is 2% to 4% per year in adults and 4% to 6% per year in children and adolescents. Risk factors that identify a high-risk population in patients with HCM include prior SCA, family history of SCD, sustained or nonsustained VT (NSVT), syncope, a drop in blood pressure with exercise, and septal hypertrophy ≥ 30 mm. Myocardial scar, detected by late gadolinium enhancement on magnetic resonance imaging (MRI), is also emerging as a predictor of risk. SCD usually results from ventricular arrhythmias, but occasionally it may be precipitated by atrial fibrillation, bradyarrhythmias, or myocardial ischemia.
- 3. Arrhythmogenic right ventricular dysplasia (ARVD).** ARVD is a rare genetic disorder characterized by heart failure, ventricular arrhythmias, and SCD. Mutations involving the desmosome are manifested by fibrofatty infiltration of the right ventricle. The incidence of SCD is approximately 2% per year and is mainly due to ventricular tachyarrhythmia. Patients are identifiable by right bundle branch block (RBBB), T-wave inversion in V_1 through V_3 and epsilon waves on the electrocardiogram (ECG), regional right ventricular akinesia, dyskinesia, or aneurysm on echo or MRI, and findings on endomyocardial biopsy.

C. The channelopathies

- 1. The congenital long QT syndrome (LQTS).** LQTS is a familial disease with a prevalence of about 1:2,000, characterized by an abnormally long QT interval, leading to the development of early afterdepolarizations and torsades de pointes.

The two variants of the syndrome include the more common autosomal dominant form (Romano-Ward syndrome) and the less common recessive form (Jervell and Lange-Nielsen syndrome), which is associated with congenital deafness. To date, mutations at 12 different LQTS susceptibility genes have been identified. The most common, accounting for over 50% of cases, is a mutation in *KCNQ1*, which encodes the α -subunit of the potassium channel conducting the slow delayed rectifier current (I_{Kr}). This mutation produces LQT1, which is characterized clinically by broad-based T waves and exercise-induced arrhythmic events (especially swimming). LQT2 (35% to 40% of cases) is caused by mutations in the *KCNH2* gene encoding the HERG protein (I_{Kr} current) and presents with low-amplitude, notched T waves and auditory arrhythmogenic triggers. LQT3 is caused by a gain-of-function mutation in the sodium channel gene *SCN5A* and manifests a long, isoelectric ST segment and SCD events during sleep.

The mortality rate for LQTS is estimated to be about 1% per year. High-risk patients include those with a corrected QT interval > 500 milliseconds, a history of syncope or SCA, male sex in children and female sex in adults (especially after menopause), and the LQT2 or LQT3 genotype. It has been postulated that 11% to 13% of sudden infant death syndrome cases could be caused by LQTS. All patients are treated with β -blocker therapy; however, genotype-specific and individualized therapies are evolving. Symptomatic patients who are either refractory to or intolerant of medical therapy, or who have other high-risk markers for SCD, should be considered for implantable cardioverter-defibrillator (ICD) implantation and left cardiac sympathetic denervation. It seems increasingly likely that many patients who suffer cardiac events due to drug-induced or other acquired QT prolongation have a *forme fruste* of LQTS.

The very rare *short QT syndrome* is caused by mutations in genes encoding the potassium channel, resulting in shortening of the action potential duration and vulnerability to VF.

2. **Brugada syndrome.** The *Brugada syndrome* is an autosomal dominant arrhythmogenic disorder caused by mutations in the *SCN5A* gene encoding the cardiac sodium channel, which predisposes patients to develop polymorphic VT or VF. The arrhythmias commonly occur at rest or during sleep, and the risk of SCA is up to 30% at 3 years in untreated symptomatic patients. Incomplete RBBB with coved ST elevation in the right precordial leads is diagnostic and, although often transient, may be elicited by a drug challenge. Atrial fibrillation and conduction abnormalities are frequently associated. Symptomatic patients (syncope or SCA) should undergo ICD implantation; risk stratification for asymptomatic patients is controversial.
3. **Catecholaminergic polymorphic ventricular tachycardia (CPVT)** is due to mutations in the ryanodine receptor and calsequestrin and results in a malignant phenotype of bidirectional VT during emotional or physical stress. Treatment is with β -blockers and ICD, and recent evidence suggests an emerging role for flecainide.

D. Others. The risk of SCD is also higher in patients with *Wolff-Parkinson-White (WPW) syndrome*, especially if they have rapidly conducting accessory pathways, when atrial fibrillation can be associated with very rapid ventricular rates and degeneration to VF. An RR interval ≤ 220 milliseconds during spontaneous AF indicates a higher risk. The incidence of SCD is 0.05% to 0.1% per year and is higher in males in their second and third decades, but the phenomenon is easily identifiable and manageable. When no cause of SCA can be found, the label *idiopathic VF* is applied. In some cases, VF is triggered by a PVC which is amenable to catheter ablation. Recent evidence suggests that *early repolarization* on ECG denotes a higher risk of SCD in the presence of proarrhythmic triggers, and the clinical implications of this are still being clarified. Some of the other cardiac and noncardiac causes of SCD are presented in Table 23.1.

TABLE 23.1 Some Other Conditions with an Increased Risk of Sudden Cardiac Death

Cardiac	Noncardiac
Cardiac vascular	Neurologic
Coronary artery anomalies	Epilepsy
Coronary artery embolism	Hereditary muscular dystrophies
Coronary arteritis (polyarteritis nodosa and Kawasaki syndrome)	Friedreich's ataxia
Coronary artery dissection	Central nervous system injury
Coronary spasm	Respiratory
Myocardial bridging	Asthma
Valvular and great vessels	Obstructive sleep apnea
Severe aortic stenosis	Massive pulmonary embolism
Severe mitral regurgitation	Pulmonary hypertension
Prosthetic valvular obstruction or dehiscence	Endocrine and metabolic
Ruptured sinus of Valsalva aneurysm	Diabetes mellitus
Aortic dissection	Acromegaly
Electrophysiologic	Electrolyte disturbances
Progressive cardiac conduction disease (Lev-Lenegr disease)	Acid-base disturbances
Myocardial	Renal
Left ventricular hypertrophy	Chronic kidney disease
Infiltrative disease (sarcoid and amyloid)	Hemodialysis
Apical ballooning syndrome	Psychiatric/psychological
Myocarditis	Depression
Congenital	Anxiety
Eisenmenger physiology	Anorexia nervosa
Late after surgical repair, especially of tetralogy of Fallot	Intense emotion
Trauma	Situational
Cardiac tamponade	Intense exercise and athletes
<i>Commotio cordis</i>	Drugs
	Antiarrhythmic drugs
	Typical and atypical antipsychotics
	Other QT-prolonging drugs
	Drug-drug interactions
	Cigarette smoking
	Cocaine

III. DIAGNOSTIC AND PROGNOSTIC TESTING. Survivors of SCA should have a detailed cardiovascular evaluation. Reversible precipitating factors must be identified and corrected. Underlying diseases must be identified and managed, and the risk of recurrent SCD must be determined. Diagnostic and prognostic testing appropriate for the survivor of SCA includes the following:

- A. **ECG** for the evidence of MI or ischemia, intraventricular conduction delay, accessory pathway (WPW syndrome), prolonged QT interval, epsilon waves, Brugada pattern, and left ventricular hypertrophy.
- B. **Laboratory data** to rule out reversible causes, such as cardiac biomarkers (creatine kinase-myocardial band, troponin T, and troponin I), abnormal electrolytes, antiarrhythmic drug levels for toxicity, and urine screening for illicit drugs such as cocaine.
- C. **ECG monitoring** to assess frequency, duration, and symptomatology of arrhythmias.

- D. **Twenty-four-hour ambulatory electrocardiography** during normal activities can be useful in predicting the risk of recurrent SCA.
- E. **Echocardiography** for the assessment of left ventricular function, valvular disease, cardiomyopathy, and hypertrophy. Nuclear or angiographic determinations of left ventricular function may be used but do not provide as much information as echocardiography. The LVEF continues to be the most potent predictor of SCD, behaving as a continuous variable with markedly increased risk $< 40\%$. However, nonsudden death also increases with declining EF, meaning that the likely mode of death cannot be predicted. LVEF is also limited by poor sensitivity—from 22% to 59% in studies in the last decade.
- F. **Coronary angiography** for the assessment of CAD or coronary anomalies.
- G. **Exercise or pharmacologic stress testing** with radionuclide imaging or echocardiography if CAD is present and myocardial ischemia and/or viability is in question.
- H. **Electrophysiologic (EP) testing** has a limited role in assessing the survivor of SCA. Given its low sensitivity, a negative test does not exclude recurrent SCA, and almost all patients who survive SCA are in any case candidates for an ICD. Although EP testing can be performed to guide programming of the ICD, this is rarely done in practice. Voltage mapping has been used to corroborate a diagnosis of ARVD, and mapping and ablation are essential in the management of patients with WPW and selected patients with cardiomyopathy and VT. Emerging applications of ablation in ARVD and Brugada syndrome deserve further study.
- I. **Cardiac MRI.** Particularly for the patient with normal left ventricular function, cardiac MRI may be useful to evaluate for arrhythmogenic right ventricular cardiomyopathy and to investigate left ventricular hypertrophy.
- J. Drug challenge with flecainide, procainamide, or ajmaline to provoke the Brugada pattern should be considered in all SCA survivors where the above tests do not reveal a cause. Epinephrine infusion or exercise testing has been used to diagnose LQT1 and CPVT.
- K. Genetic testing for the channelopathies, HCM, and ARVD is becoming increasingly comprehensive; however, many as yet unidentified mutations are postulated to exist. At present, only 21% of patients with Brugada syndrome and 52% with ARVD have an identifiable causative mutation. Testing in cases where a clear phenotype has not been established, or is not suggestive of a genetic disorder, is discouraged, as many variants are of uncertain significance. A positive genetic test is useful and facilitates family screening, but a negative test is not.

IV. THERAPY

A. Acute therapy for SCA

1. **Cardiopulmonary resuscitation (CPR).** Early response is crucial. The two most critical components of out-of-hospital cardiac resuscitation are the availability of a rapid response system and citizen bystander CPR. Survivors of SCA are more likely to be discharged from the hospital if the arrest is witnessed and they receive early CPR from bystanders. There is an increasing drive to train police personnel, students, and the general public in resuscitation techniques, focusing on high-quality, uninterrupted chest compressions.
2. **Automated external defibrillator (AED) and public access defibrillation.** An AED is designed to be used by emergency personnel and lay rescuers with minimal or no training, particularly for victims of out-of-hospital SCA. The device monitors the patient's ECG via self-adhesive defibrillation electrode pads applied to the chest wall and is programmed with a VF detection algorithm. When the device detects VF, an alarm is emitted, followed by delivery of a defibrillation shock or an indicator for the rescuer to press a button to deliver the shock. Availability of these devices results in more rapid delivery of defibrillation and improved survival to hospital discharge in several large trials. Provision of AEDs for public access defibrillation in airports, sporting facilities, and shopping

malls has the potential to have a significant impact on survival of out-of-hospital SCA. Home AEDs have not been shown to increase survival.

3. **Advanced cardiac life support (ACLS).** Unlike AEDs, incorporation of ACLS techniques into prehospital care has not been shown to improve survival in out-of-hospital SCA. Continuous refinements in ACLS algorithms continue to be made, including an emphasis on high-quality CPR with minimal interruption.
4. **Post-cardiac arrest hospital care.** Initial management is focused on establishing and maintaining hemodynamic stability and supportive care. Amiodarone or lidocaine (especially if ischemia is suspected as the trigger) is often used to prevent further ventricular tachyarrhythmias. Therapeutic hypothermia for patients who remain unconscious after resuscitation confers a modest improvement in neurologic outcome. Immediate coronary angiography, with revascularization if indicated, may improve survival in patients in whom an ischemic etiology is suspected. Further diagnostic testing is described above.

B. Primary prevention of SCD

1. **Identifying individuals at risk for SCD.** No single factor has been identified that accurately predicts the occurrence of SCD, although combinations of factors have been more useful. In general, the specificity and positive predictive value of these tests are poor, whereas the negative predictive value is much better (particularly for combinations of tests). Overall, the most potent predictor of survival continues to be LVEF, but other factors may aid prognostication and guide subsequent therapy. Other tools for predicting the risk of SCD, such as EP testing, ambulatory electrocardiography, signal-averaged electrocardiography (SAECG), baroreflex sensitivity, heart rate variability (HRV), and T-wave alternans, have been used to identify high-risk groups, but none have been shown to be of convincing value. Although a combination of different tests can improve sensitivity and specificity, the positive predictive value remains modest.
2. **Pharmacologic agents and surgical/percutaneous revascularization.** Because the majority of episodes of SCD occur in patients with CAD, agents that reduce myocardial ischemia (β -blockers), prevent or limit the extent of MI, and alter ventricular remodeling after MI (ACE inhibitors and aldosterone antagonists) have all been shown to reduce the incidence of SCD. Although there is no direct evidence of a role for antiplatelets or statins in reducing SCD, such an effect is likely, given the reduction in mortality in several broad populations. Early studies of surgical myocardial revascularization showed a reduction in SCD for patients with triple-vessel CAD and left ventricular dysfunction compared with those patients treated medically. Fibrinolysis and percutaneous coronary intervention also reduce SCD in patients with MI. Catheter ablation of VT has a role in select patient populations, particularly in patients with incessant arrhythmias, despite antiarrhythmic drug and/or implantable device therapy.

More than 40 years ago, complex ventricular ectopy in survivors of MI was recognized as a risk factor for SCD. Suppression of ventricular ectopy with antiarrhythmic drugs in such patients was, therefore, thought to be beneficial. However, the Cardiac Arrhythmia Suppression Trial (CAST) demonstrated that the proarrhythmic effects of class Ic antiarrhythmic drugs are greater than the benefit achieved through ectopy suppression in the post-MI population, resulting in a 2.6-fold increased mortality. Excess mortality was also demonstrated in survivors of MI with poor left ventricular function taking the class II/III agent sotalol in the Survival With Oral *d*-Sotalol (SWORD) study and with mexiletine.

To date, of all the antiarrhythmic drugs only amiodarone has been shown to reduce SCD in some populations. Initial small trials of amiodarone therapy for survivors of MI, and meta-analyses of these trials, suggested reduced SCD mortality and the larger but unblinded Grupo de Estudio de la Sobrevida en la Insuficiencia Cardíaca en Argentina (GESICA) study appeared to corroborate

this finding. However, several prospective, placebo-controlled trials did not. The Survival Trial of Amiodarone in Patients with Congestive Heart Failure (CHF-STAT) failed to demonstrate a significant reduction in either SCD or all-cause mortality in a largely male population with heart failure, $EF \leq 40\%$, and frequent PVCs. Although the European Myocardial Infarct Amiodarone Trial (EMIAT) demonstrated a 35% reduction in arrhythmic deaths in a population with recent MI, there was no difference in all-cause mortality. The Canadian Amiodarone Myocardial Infarction Arrhythmia Trial (CAMIAT) similarly reported a reduction in resuscitated VF or arrhythmic death in survivors of MI with frequent ventricular ectopy, but no difference in all-cause mortality. Lastly, there was no difference in the primary end point of all-cause mortality between amiodarone and placebo in the medical treatment arm of the large Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT). The newer benzofuran derivative, dronedarone, also reduced SCD in the pivotal ATHENA trial of patients with atrial fibrillation and additional risk factors, but increased all-cause mortality in patients with severe heart failure in the Antiarrhythmic Trial with Dronedarone in Moderate to Severe CHF Evaluating Morbidity Decrease (ANDROMEDA). Mexiletine showed a trend toward increased mortality, and dofetilide and azimilide had no effect on all-cause mortality or SCD in patients with recent MI in large controlled studies.

In summary, amiodarone reduces SCD but not all-cause mortality in patients with heart failure or recent MI, and several other antiarrhythmics, including class Ic agents, mexiletine, dronedarone, and sotalol, may increase mortality in this population.

- 3. Implantable devices.** In light of the inefficacy and even hazards of antiarrhythmic drugs for the prevention of SCD, attention has shifted to the ICD. Since its introduction by Mirowski in 1980, technical refinements have paralleled a series of clinical trials which extended indications to primary prevention in select populations. The Multicenter Automatic Defibrillator Implantation Trial (MADIT) demonstrated a 54% relative risk reduction in all-cause death versus usual care in 196 patients with prior MI, New York Heart Association (NYHA) class I–III heart failure, $EF \leq 35\%$, NSVT, and inducible, nonsuppressible, ventricular arrhythmia during EP study (EPS). The Multicenter Unsustained Tachycardia Trial (MUSTT) randomized patients with coronary artery disease, $EF \leq 40\%$, NSVT, and inducible VT/VF to receive EP-guided antiarrhythmic drug therapy, with or without an ICD, or no therapy. The 27% reduction in arrhythmic death or cardiac arrest in the EP-guided drug therapy arm was entirely driven by a 76% reduction in patients with ICDs, with no difference between drug therapy and no therapy. Given the modest predictive value of EPS, MADIT II dispensed with inducible VT as an inclusion criterion and enrolled patients with prior MI on the basis of an $EF \leq 30\%$. This randomized comparison of ICD with usual care demonstrated a 31% relative risk reduction in all-cause mortality over an average follow-up of 20 months. MADIT, MUSTT, and MADIT II all enrolled patients with prior MI. While the underpowered Amiodarone Versus Implantable Cardioverter-Defibrillator (AMIOVIRT) and Cardiomyopathy Trial (CAT) failed to show a benefit of ICDs over medical therapy in patients with nonischemic cardiomyopathy (NICM), the results of the Defibrillators in Nonischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial extended primary prevention ICD therapy to these patients. In patients with NICM, heart failure, $EF \leq 35\%$, and NSVT or frequent PVCs, a nonsignificant reduction in all-cause mortality was observed, with a significant reduction in SCD. The larger SCD-HeFT randomized 2,521 patients with ischemic cardiomyopathy (52%) or NICM (48%), $EF \leq 35\%$, and NYHA functional class II or III heart failure to receive conventional therapy plus placebo,

amiodarone, or a single lead ICD. ICD therapy reduced all-cause mortality by 23% compared with placebo, whereas amiodarone was not associated with any benefit. These trials, and SCD-HeFT in particular, ushered in the current era of primary prevention ICDs for patients risk-stratified largely on the basis of EF.

The limitations of ICDs have also been defined by clinical trials. The Coronary Artery Bypass Graft (CABG) Patch Trial demonstrated that primary prevention ICD implantation at the time of CABG in patients with preoperative left ventricular dysfunction ($EF \leq 35\%$) and an abnormal SAECG did not improve the overall survival, despite reducing arrhythmic deaths. The lower event rates in the CABG Patch Trial were consistent with earlier evidence that CABG reduces the risk of SCD in this population, negating the protective effect of the ICD.

MADIT, MUSTT, and MADIT II studied patients with remote (> 3 weeks) ischemic events. The Defibrillator in Acute Myocardial Infarction Trial (DINAMIT) assessed whether the benefits of ICD therapy would also be seen early after MI. The trial enrolled patients 6 to 40 days post-MI with $EF < 35\%$ and impaired HRV or elevated average 24-hour heart rate and randomized them to receive an ICD or no ICD. Although ICD therapy reduced arrhythmic death, this was offset by an increase in nonarrhythmic death in the ICD group, so there was no difference in all-cause mortality over 30 months of follow-up. These results were confirmed by the larger Immediate Risk Stratification Improves Survival (IRIS) trial, which enrolled a similar population. Taken together, IRIS and DINAMIT suggest that while ICDs prevent SCD in high-risk patients early post-MI, this merely changes the mode of death to nonsudden death, without affecting the overall survival. This is supported by a secondary analysis of DINAMIT, which showed that the risk of nonsudden death in the ICD group was 4.8-fold higher in those who had received an appropriate shock. The above findings have been incorporated into the Centers for Medicare and Medicaid Services (CMS) coverage determination for ICDs, which excludes patients with MI within 40 days and surgical or percutaneous revascularization within 3 months of ICD implantation. A wearable defibrillator is available for temporary use, while diagnostic testing is ongoing, or during periods of transient elevated risk.

4. **Cardiac resynchronization therapy (CRT).** Approximately 30% of patients with advanced heart failure ($EF \leq 35\%$) have an associated ventricular conduction delay resulting in a QRS duration ≥ 120 milliseconds and are candidates for CRT. Biventricular pacing has been shown to improve survival, quality of life, exercise capacity, and EF in patients with advanced CHF. Extended follow-up data from the Cardiac Resynchronization in Heart Failure (CARE-HF) trial also reported a significant 46% reduction in SCD in patients with CRT without a defibrillator when compared with no CRT. However, a significant number of SCDs occurred in the CRT group, some of which might conceivably have been prevented by a defibrillator. The only large randomized trial comparing CRT with a defibrillator (CRT-D), CRT without (CRT-P), and no device was the Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure (COMPANION) trial. While not powered to detect a difference between CRT-D and CRT-P, a nonsignificant 50% decrease in SCD was seen with CRT-D in patients with NYHA class III or IV CHF, $EF \leq 35\%$, and a QRS duration ≥ 120 milliseconds. These data suggest that CRT-D should be considered for most patients eligible for biventricular pacing.

C. Secondary prevention

1. **Pharmacologic agents.** As with primary prevention of SCD, the disappointing efficacy and safety of class I antiarrhythmic drugs shifted attention to other antiarrhythmic drugs for the secondary prevention of SCD. In the Cardiac Arrest in Seattle Conventional Versus Amiodarone Drug Evaluation (CASCADE) study,

amiodarone reduced cardiac death, arrest, and ICD shocks compared with conventional class I antiarrhythmic drugs in a secondary prevention population. In addition, the Electrophysiologic Study Versus Electrocardiographic Monitoring (ESVEM) trial demonstrated that the class II/III antiarrhythmic drug sotalol was superior to six class I agents guided by EP testing or Holter monitoring in preventing all-cause, cardiac, and arrhythmic mortality in patients with a history of VT/VF, SCA, or syncope. However, emergence of the ICD led to randomized trials comparing the efficacy of best medical therapy and ICDs for the secondary prevention of SCD.

2. **Implantable devices.** The Antiarrhythmics Versus Implantable Defibrillators (AVID) trial studied the efficacy of ICD therapy versus the antiarrhythmic drugs amiodarone or sotalol for the secondary prevention of SCD in patients with resuscitated VF or sustained VT plus either syncope or $EF \leq 40\%$ and hemodynamic compromise during VT. Inducible arrhythmias were not required for inclusion, and only sotalol therapy was guided by EP testing (only 2.6% of patients randomized to antiarrhythmic drug therapy were discharged on sotalol). ICDs reduced all-cause mortality by 31% at 3 years of follow-up.

Two other large trials of ICDs for secondary prevention of SCD that ran concurrently with AVID reported similar results. The Cardiac Arrest Study Hamburg (CASH) found that ICDs conferred a nonsignificant 23% reduction in all-cause mortality when compared with amiodarone or metoprolol in patients with resuscitated cardiac arrest due to documented VT/VF. The propafenone arm of the study was terminated early after an interim analysis showed excess mortality compared with the ICD group. The Canadian Implantable Defibrillator Study (CIDS) enrolled a similar population as the AVID trial randomizing patients with resuscitated VF, sustained VT with syncope or hemodynamic compromise and $EF \leq 35\%$, or unmonitored syncope with subsequent spontaneous or induced VT to ICD or amiodarone therapy. Over a mean follow-up period of 3 years, a nonsignificant 19.7% relative risk reduction in all-cause mortality was observed, as well as a nonsignificant 32.8% reduction in SCD. Each of the above studies excluded patients with a transient or reversible cause of ventricular arrhythmias, such as MI within 72 hours, or electrolyte imbalances. A meta-analysis of these three trials confirmed a significant 28% reduction in the relative risk of death with the ICD, which was due largely to a 50% reduction in SCD.

Of considerable interest is evidence that patients screened for the AVID trial but thought to have a transient or reversible cause of SCA, and who were not entered in the trial but followed in a registry, had poor long-term survival similar to those patients who were also ineligible for the trial but known to be at high risk for SCD. These data emphasize the need for meticulous evaluation of every SCA survivor and careful consideration of whether SCA was due to a cause that was not only transient and reversible but also preventable in the future.

- D. **Summary: antiarrhythmic drugs versus ICDs.** Current guidelines for ICD therapy are summarized in Table 23.2. From the available data, there is good evidence that many antiarrhythmic drugs are not efficacious and may be harmful in the primary prevention of SCD, and antiarrhythmic drugs (apart from β -blockers) are not indicated for this purpose. ICD therapy has been proven to be highly effective in the termination of malignant ventricular arrhythmias and is more effective than antiarrhythmic medications for the prevention of SCD in patients with ischemic or nonischemic heart failure and an $EF \leq 35\%$. Patients with prolonged QRS duration, especially with LBBB, should also be considered for CRT. The most powerful predictor of SCD risk in this population remains LVEF, and other methods such as EP testing and SAECG may give additional information but are neither sensitive nor specific enough to select patients for ICD therapy. Specific antiarrhythmics may have niche uses in high-risk patients with genetic diseases predisposing

TABLE 23.2 **Indications for Implantable Cardioverter–Defibrillator Therapy**
Class I

1. Survivors of cardiac arrest due to VF or hemodynamically unstable sustained VT after evaluation to define the cause of the event and to exclude any completely reversible causes
2. Structural heart disease and spontaneous sustained VT, whether hemodynamically stable or unstable
3. Syncope of undetermined origin with clinically relevant, hemodynamically significant sustained VT or VF induced during electrophysiologic study
4. LVEF $\leq 35\%$ due to prior MI, at least 40 d post-MI, and NYHA class II or III
5. Nonischemic DCM, LVEF $\leq 35\%$, and NYHA class II or III
6. LV dysfunction due to prior MI, at least 40 d post-MI, LVEF $\leq 30\%$, and NYHA class I
7. Nonsustained VT due to prior MI, LVEF $\leq 40\%$, and inducible VF or sustained VT during electrophysiologic study
8. Symptomatic sustained VT in association with congenital heart disease after hemodynamic and electrophysiologic evaluation

Class IIa

1. Unexplained syncope, significant LV dysfunction, and nonischemic DCM
2. Sustained VT and normal or near-normal ventricular function
3. Hypertrophic cardiomyopathy with one or more major risk factors for SCD
4. ARVD/C with one or more risk factors for SCD
5. Long QT syndrome with syncope and/or VT while receiving β -blockers
6. Nonhospitalized patients awaiting heart transplantation
7. Brugada syndrome with syncope
8. Brugada syndrome with documented VT that has not resulted in cardiac arrest
9. Catecholaminergic polymorphic VT with syncope and/or documented sustained VT while receiving β -blockers
10. Cardiac sarcoidosis, giant cell myocarditis, or Chagas disease
11. Congenital heart disease with recurrent syncope of undetermined origin in the presence of either ventricular dysfunction or inducible ventricular arrhythmias during electrophysiologic study

Class IIb

1. Nonischemic heart disease, LVEF $\leq 35\%$, and NYHA class I
2. Long QT syndrome with risk factors for SCD
3. Syncope and advanced structural heart disease where thorough invasive and noninvasive investigations have failed to define a cause
4. Familial cardiomyopathy associated with sudden death
5. LV noncompaction

TABLE 23.2 Indications for Implantable Cardioverter–Defibrillator Therapy (Continued)

6. Recurrent syncope associated with complex congenital heart disease and advanced systemic ventricular dysfunction when thorough invasive and noninvasive investigations have failed to define a cause

Class III

1. Patients who do not have a reasonable expectation of survival with an acceptable functional status for at least 1 y
2. Incessant VT or VF
3. Patients with significant psychiatric illnesses that may be aggravated by device implantation or that may preclude systematic follow-up
4. NYHA class IV patients with drug-refractory congestive heart failure who are not candidates for cardiac transplantation or CRT-D
5. Syncope of undetermined cause without inducible ventricular tachyarrhythmias and without structural heart disease
6. VF or VT that is amenable to surgical or catheter ablation (e.g., atrial arrhythmias associated with the Wolff-Parkinson-White syndrome, RV or LV outflow tract VT, idiopathic VT, or fascicular VT in the absence of structural heart disease)
7. Ventricular tachyarrhythmias due to a completely reversible disorder in the absence of structural heart disease (e.g., electrolyte imbalance, drugs, or trauma)

VF, ventricular fibrillation; VT, ventricular tachycardia; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NYHA, New York Heart Association; DCM, Dilated cardiomyopathy; SCD, sudden cardiac death; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; CRT-D, cardiac resynchronization therapy with a defibrillator; RV, right ventricle; LV, left ventricle.

Adapted from the 2008 ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities.

to SCD, such as HCM, ARVD, Brugada syndrome, and LQTS, and an ICD is also indicated in select patients. The bradyarrhythmias respond well to pacemaker therapy. Radiofrequency catheter ablation is the therapy of first choice in patients with WPW syndrome and is an effective synergistic therapy in patients with VT who have recurrent ICD shocks.

Evidence from several recent randomized trials demonstrates the superiority of the ICD over antiarrhythmic drugs for the population requiring secondary prophylaxis. Antiarrhythmic drugs such as amiodarone, sotalol, and mexiletine may be of use in those patients who experience frequent ICD shocks.

V. PROGNOSIS

- A. VF and pulseless VT (“shockable rhythms”) are the initial rhythm in approximately one-quarter of SCA victims and are associated with more favorable outcomes than asystole or PEA. VT/VF incidence declines by ~10% with each minute since the onset of SCA; therefore, witnessed SCA and prompt recognition and defibrillation are associated with improved survival. Only one-third of SCA victims receive bystander CPR. A recent large study of cardiac arrest incidence and outcomes in North America found that of the 58% of patients in whom resuscitation was attempted, 7.6% survived to hospital discharge, with wide regional

variation. This proportion rose to 21% if the initial rhythm was VF. A number of factors have been identified to aid prognostication post arrest, including preexisting comorbidities, absent pupillary and corneal reflexes, extensor or no motor response to pain on day 3, and myoclonus status epilepticus; however, none are definitive.

VI. FUTURE. Large population studies are needed to better define the incidence of SCD across ethnic/racial groups and elucidate the mechanisms. Discovery of risk markers of SCD in the general population, such as clinical, molecular, and genetic factors, will facilitate targeting of evaluation and therapy to those who need it. Coronary artery disease and its consequences account for 80% of SCD, often occurring as the first presentation of CAD. Given the difficulty in identifying those with subclinical disease who are ostensibly at low risk, focus has recently moved to primordial prevention—the prevention of the development of risk factors for CAD. This will likely have the most impact on SCD at the population level, but its effects are difficult to measure. In those at established risk, improved risk markers that refine the current LVEF-based approach will allow better targeting of ICD therapy.

ACKNOWLEDGMENTS: *The author thanks Drs. Bryan Baranowski, Mandeep Bhargava, and Robert A. Schweikert for their contributions to earlier editions of this chapter.*

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WEB SITES

- Get with the Guidelines – Resuscitation. American Heart Association, Dallas, TX. www.nrcpr.org
- QT Drug Lists. Arizona Center for Education and Research on Therapeutics, The Critical Path Institute, Tucson, AZ and Rockville, MD. <http://www.azcert.org/index.cfm>

Atrial Fibrillation

I. INTRODUCTION. Atrial fibrillation (AF) is the most common sustained tachyarrhythmia and is associated with increased cardiovascular morbidity, mortality, and preventable stroke, accounting for approximately one-third of cardiac hospitalizations for cardiac rhythm disturbances. The incidence and prevalence of AF increase with age, with a prevalence of 0.4% to 1% in the general population and as high as 8% in patients older than 80 years. In addition, the age-adjusted incidence in the Framingham study has increased significantly from the 1960s to the present. It is estimated that 3 million people in America and 6 million people in Europe have either paroxysmal AF or persistent AF. AF is associated with increased risk of stroke, heart failure exacerbation, and all-cause mortality, especially in women. The mortality rate in patients with AF is about twice that of patients with normal sinus rhythm (NSR).

A. Classification. AF may be classified as lone, idiopathic, first detected, recurrent, paroxysmal, persistent, long-standing persistent, and permanent. **Lone AF** is used to describe patients experiencing AF without clinical or echocardiographic evidence of cardiopulmonary disease. **Idiopathic AF** refers to the uncertainty of AF origin without considering age or underlying cardiovascular pathology. During a patient's first detected episode of AF, it should be noted whether it is self-limited or the patient symptomatic with the arrhythmia. When a person has experienced two or more episodes of AF it is considered **recurrent**, and once recurrent AF is terminated it is referred to as **paroxysmal**. Paroxysmal episodes are usually self-terminating and, at least initially, do not usually require direct current cardioversion (DCC). **Persistent AF** usually lasts longer than 7 days and requires cardioversion for its termination. **Long-standing persistent** is when AF has lasted for > 1 year. AF becomes **permanent** once cardioversion, either electrical or chemical, is unsuccessful and presence of arrhythmia is accepted by the patient and physician and hence rhythm control interventions are not pursued.

B. Clinical presentation. As with all arrhythmias, the clinical presentation of AF can vary widely and **patients may be asymptomatic**, despite rapid rates of ventricular response. Common symptoms include **palpitations, fatigue, dyspnea and/or shortness of breath, dizziness, and diaphoresis**. Less commonly, patients may present with extreme manifestations of hemodynamic compromise, such as **chest pain, pulmonary edema, and syncope**. AF is often noted in patients presenting with a new thromboembolic stroke, with reported rates of 10% to 40%.

C. Differential diagnosis. AF needs to be distinguished from multifocal atrial tachycardia (MAT), frequent premature atrial contractions, and automatic atrial tachycardias.

D. Etiology. AF is most commonly associated with advanced age, hypertension, valvular heart disease, congestive heart failure (CHF), and coronary artery disease (CAD). The pathophysiology is dependent on the interaction between atrial anatomic and physiologic factors that favor the initiation and maintenance of the arrhythmia. Pathophysiologically, these entities result in left atrial fibrosis, pulmonary vein dilation, and reduced atrial contractility, which in turn result at a cellular

level in abnormal intracellular calcium handling, atrial myolysis, connexin down-regulation, and altered sympathetic innervation. Structural remodeling results in electrical dissociation between muscle bundles and local conduction heterogeneities facilitating the initiation and perpetuation of AF. This electroanatomical substrate permits multiple small reentrant circuits that can stabilize the arrhythmia and lead to the establishment of AF.

AF has been associated with physiologic stress, drugs, pulmonary embolism, chronic lung disease, hyperthyroidism, caffeine, infectious processes, and various metabolic disturbances. AF has also been linked with obesity and likely underlying sleep-disordered breathing. This phenomenon seems to be mediated by left atrial dilation. Other less common cardiac associations include Wolff-Parkinson-White (WPW) syndrome, pericarditis, and cardiomyopathy. Surgery, particularly **cardiac surgery, is associated with a high risk of postoperative AF** that depends on the type of cardiac surgery and is highest for mitral valve surgery, which may reach 35% to 50%. Persistence of AF has been correlated with elevated C-reactive protein levels, which raises the question of a role for inflammation in this condition, and atrial natriuretic peptide has been found to be elevated in people with acute AF. This hormone, which is released by myocardial tissue in response to increased wall stress, promotes diuresis and vasodilation. However, with long-standing AF, atrial natriuretic peptide levels remain within the normal range and patients do not experience its useful hemodynamic effects.

E. Pathophysiology

1. The role of the pulmonary veins as a source of triggers and/or drivers in AF is increasingly appreciated. A previous model proposed by Moe et al. in 1962 had described multiple reentrant wavelets within the atrial tissue (substrate) that contributed to the maintenance of AF. Recent data support **a focal mechanism involving both increased automaticity and multiple reentrant wavelets, occurring predominantly in the left atrium around the pulmonary veins**. A new model incorporates these mechanisms of initiators/drivers of AF and atrial substrate conditions for AF maintenance. This in turn may be affected by various modulating factors, such as autonomic tone, medications, atrial pressure, and catecholamine levels. AF is a very complex arrhythmia, and this mechanistic model simply serves to provide a conceptual framework from which to gain insight into it.
2. Paroxysmal, persistent, or chronic AF presents a **considerable risk for thromboembolism**; lone AF is presently thought to also increase the risk, but to a lesser extent. **The risk of stroke becomes more pronounced with increased age**. An increased risk of stroke has been shown to be associated with AF in the presence of any of the following: **age > 65 years, history of diabetes, history of hypertension, history of CHF, history of prior stroke, or transient ischemic attacks (TIAs)**. Left ventricular (LV) systolic dysfunction predicts ischemic stroke in patients with AF who do not receive antithrombotic therapy.

F. Laboratory examination and diagnostic testing.

The initial evaluation of a patient with new-onset AF includes at a minimum a detailed history including enquiry about family history of AF and physical examination to define the clinical type of AF—frequency, duration, and precipitating factors—and to delineate the presence and nature of symptoms associated with AF. In addition, evaluation should include the following:

1. **A 12-lead electrocardiogram (ECG)** to identify the rhythm (that is to verify AF), underlying LV hypertrophy, and presence of preexcitation, and to diagnose the existence of CAD and any other atrial arrhythmias. A 12-lead ECG may also be used to measure and follow PR, QRS, and QT intervals during the treatment with antiarrhythmic agents. In AF the P waves are absent. Atrial activity is chaotic and fibrillatory (**F waves are present**). The baseline of the ECG is often

undulating and may occasionally have coarse, irregular activity that can resemble atrial flutter, but it is not as stereotypical from wave to wave as atrial flutter. AF is distinguished from MAT by the presence in MAT of at least three different morphologic types of P waves. **Ventricular rhythm is usually irregularly irregular, and if AF is suspected with a regular ventricular response, then heart block with a junctional or ventricular escape should be considered.** The **atrial rate** is generally in the **range of 400 to 700 beats/min**, while the ventricular response is generally in the range of 120 to 180 beats/min in the absence of drug therapy. Ventricular response may be 180 beats/min or greater in the presence of an accessory pathway.

2. **Transthoracic echocardiogram** is usually performed to identify the presence of valvular heart disease, to assess atrial and ventricular size and function, and to document coexistent pulmonary hypertension. Echocardiography is also used as a prognostic tool to predict the development of systemic complications from AF and to help in the decision to initiate antithrombotic therapy. **Echocardiographic predictors of increased thromboembolic risk include mitral stenosis, left atrial enlargement, reduced LV systolic function, decreased left atrial appendage emptying velocities, and evidence of spontaneous contrast (“smoke”) or thrombus in the left atrium or left atrial appendage.**
 3. **Tests of thyroid, renal, and hepatic function.** Hyperthyroidism should always be considered, especially when the ventricular rate is difficult to control.
 4. Additional investigation in selected patients with AF may include ambulatory ECG monitoring (e.g., Holter), or a 6-minute treadmill walk test to document heart rate response to exercise and an evaluation of sleep-disordered breathing should be considered especially in obese patients.
- G. Therapy. The therapy of choice in any unstable patient where AF is recent in onset and contributing to the instability is immediate DCC.** The term “unstable” should include the patient who is highly symptomatic (e.g., chest pain and pulmonary edema), as well as the patient who is hemodynamically unstable. **General management of AF centers on three areas: control of the ventricular response, minimization of the thromboembolic risk, and restoration and maintenance of sinus rhythm.**

1. **Control of the ventricular response.** The ventricular response is generally **controlled through drugs** that slow conduction through the atrioventricular (AV) node. AF that presents in the setting of WPW syndrome usually has evidence of preexcitation on ECG and is treated differently from AF conducting down the AV node alone. As noted previously, **intravenous calcium channel blockers, β -blockers, adenosine, and lidocaine are contraindicated in patients with AF and WPW syndrome associated with preexcitation because they facilitate conduction down the accessory pathway, causing acceleration of the ventricular rate, hypotension, and ventricular fibrillation.** In the hemodynamically stable patient, class I antiarrhythmic medications such as procainamide may be administered intravenously, which diminishes antegrade conduction down the accessory pathway and decreases the degree of preexcitation and may convert the AF. For patients without evidence of preexcitation, the following agents are available to control the ventricular rate.
 - a. β -Blockers have a **rapid onset of action**, as well as **short half-lives in both the oral and intravenous forms.** These medications should be used cautiously in patients who have known decreased systolic function or evidence of heart failure. Intravenous preparations of metoprolol, esmolol, and propranolol have their onset of action in approximately 5 minutes. Orally available β -blockers of varying durations of action can be used for rate control. These include metoprolol and propranolol, as well as atenolol, nadolol, and a number of less commonly used agents. Amiodarone is an antiarrhythmic

medication with β -blocking properties and can be used for both rate and rhythm control in the acute setting. Sotalol is another class III antiarrhythmic medication with β -blocking properties, which can be used for both rate and rhythm control; however, this medication is available in oral form only and is more proarrhythmic than amiodarone.

- b. Calcium channel blockers such as diltiazem and verapamil are available in both intravenous and oral forms. The intravenous forms are rapidly effective and have a short duration of effect. **In appropriate patients, they provide rapid control of the ventricular response.** Both oral diltiazem and verapamil are available in short-acting and sustained-release preparations.
- c. Digitalis has long been used for rate control. Given its relatively long onset of action, **digoxin is ideally used in patients with decreased LV function or where a contraindication exists to the use of β -blockers or calcium channel blockers** (e.g., bronchospastic airway disease, asthma, or hemodynamic instability). It may be used as an adjunct to β -blockers or calcium channel blockers in patients in whom these medicines alone do not provide sufficient control of the heart rate. Digoxin is usually **effective at controlling the resting heart rate**; however, it is **less effective at lowering the ventricular response to activity**. Because of this it is recommended that if digoxin alone is used in rate control, the patient should undergo monitored exercise and the exertional heart rate verified to be < 110 beats/min.

Digoxin can be administered intravenously or orally. The **onset of action of digoxin is slow** (1 to 4 hours). Initially dosing of digoxin is 0.25 mg intravenously every 6 hours for a total of 1 mg every 24 hours. Then a maintenance dose is given, which is based on the patient's renal function. Digoxin is **generally well tolerated, although it is associated with adverse effects**, such as gastrointestinal toxicity and neurotoxicity, and because of its long half-life (38 to 48 hours) is more likely to be associated with symptomatic bradycardia requiring intervention such as temporary pacing.

- d. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor antagonists may decrease the incidence of AF by decreasing left atrial pressure and by reducing the frequency of atrial premature beats. These medications may also reduce atrial fibrosis and decrease the recurrence of AF. Withdrawal from ACE inhibitors is associated with postoperative AF in patients undergoing coronary artery bypass grafting (CABG) surgery, and concurrent therapy with ACE inhibitors and antiarrhythmic agents enhances the maintenance of sinus rhythm.
 - e. HMG-CoA reductase inhibitors: statin drugs decrease the risk of AF recurrence following cardioversion. The mechanisms underlying this are poorly understood but probably include an inhibitory effect on the progression of coronary disease as well as their pleiotropic anti-inflammatory and antioxidant properties.
 - f. Antiarrhythmic agents such as dofetilide and ibutilide are effective for conversion of atrial flutter and AF but are not effective for the control of ventricular rate alone. Propafenone, which is a class IC antiarrhythmic drug, exerts additional mild β -blocking effects and may slow conduction across the AV node, although this is seldom sufficient to control the rate in patients with AF and may paradoxically cause an increase in AV nodal conduction and accelerate the ventricular rate response. Flecainide is another class IC agent that is very effective in converting AF in structurally normal hearts but like propafenone requires concomitant AV nodal blockage.
2. **Thromboembolic risk management**
- a. Current recommendations regarding the use of antithrombotic therapy to prevent the development of thromboembolism in patients with AF are to

use antithrombotic therapy in all patients with AF except those with lone AF or with contraindications to antithrombotic agents. **Lone AF is defined as that occurring in a structurally normal heart, in a patient younger than 65 years.** The American Heart Association (AHA) recommends that the individualized selection of appropriate antithrombotic agents **associated with the highest risk of stroke in patients with AF include a history of prior thromboembolism (stroke, TIA, and systemic embolism) and rheumatic mitral stenosis.** Moderate risk factors for stroke include age older than 65 years, CAD, CHF, female gender, hypertension, diabetes mellitus, and renal insufficiency. Presence of more than one moderate risk factor suggests the use of a vitamin K antagonist with a goal international normalized ratio (INR) of 2.0 to 3.0 or or alternative anticoagulation with dabigatran, rivaroxaban or apixaban. Aspirin in doses of 81 to 325 mg daily is recommended as an alternative to vitamin K antagonism in low-risk patients or in those with contraindications to oral anticoagulation, and more recent evidence suggests that combination of aspirin and clopidogrel is superior to the use of either agent alone in patients who are unable to tolerate warfarin therapy. The guidelines also suggest similar use of antithrombotic therapy in patients with atrial flutter. Table 24.1 outlines one method of selecting the appropriate antithrombotic therapy for any given patient.

Based on the multivariate analysis from randomized controlled trials (RCTs), there have been several clinical scores developed to stratify the risk of systemic complications. The most well known of these is called the **CHADS** (Cardiac Failure, Hypertension, Age, Diabetes, and Stroke) risk index, which is a point system and assigns two points for history of TIA or stroke and one point for

TABLE 24.1 Selection of Appropriate Antithrombotic Therapy

Risk category	Recommended therapy	
No risk factors	Aspirin, 81–325 mg daily	
One moderate risk factor	Aspirin, 81–325 mg daily or warfarin (INR 2.0–3.0, target 2.5)	
Any high risk factor or more than one moderate risk factor	Warfarin (INR 2.0–3.0, target 2.5) ^a	
Less validated or weaker risk factors	Moderate risk factors	High risk factors
Gender (female)	Age ≥ 75 y	Previous stroke, TIA, or embolism
Age (65–74 y)	Hypertension	Mitral stenosis
Coronary artery disease	Heart failure	Prosthetic heart valve ^b
Thyrotoxicosis	LV ejection fraction 35% or less	
	Diabetes mellitus	

^aIf mechanical valve, target INR > 2.5.

^bMechanical prosthesis heart valve especially if in the mitral position to replace “prosthetic heart valve”

INR, international normalized ratio; LV, left ventricular; and TIA, transient ischemic attack.

Adapted from ACC/AHA practice guidelines.

each of the following risk factors: age older than 75 years, hypertension, diabetes, or recent heart failure. This risk factor index was evaluated retrospectively in patients older than 65 years and with nonvalvular AF, and the stroke risk varied from 1.8% per year in the lowest risk group with a CHADS score of 0, to 18.2% per year for those with an index score of 6. Another thromboembolic risk factor scoring system is the CHA₂DS₂-VASc, which assigns two points for age > 75 years and prior history of TIA or stroke and one point for each of the *following* risk factors: CHF, hypertension, diabetes, stroke, vascular disease, age 65 to 74 years, and female gender. Thus, this risk stratification scheme extends the CHADS₂ scheme by considering additional stroke risk factors that may influence the decision on whether or not to anticoagulate with a threshold for therapy that is similar to the CHADS scheme. An assessment of bleeding risk is an integral part of patient evaluation prior to initiating anticoagulation. A simple bleeding risk score (HAS-BLED: hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [age > 65 years], drugs/alcohol concomitantly) has been used to assess the risk of bleeding while on anticoagulant therapy. A score of ≥ 3 indicates higher risk and suggests caution and regular review of the patient following the initiation of anticoagulant therapy.

Following cardioversion, therapeutic anticoagulation should be continued until sinus rhythm has been maintained for at least 4 weeks to allow for recovery of the atrial transport mechanism and for the recurrence of AF. The decision to anticoagulate beyond 4 weeks will be dependent on the CHADS₂ score of the patient with long-term anticoagulation being recommended for all patients with a CHADS₂ score ≥ 2 . For patients with a CHADS₂ score of 1, the physician and patient should discuss the merits and risks of long-term anticoagulation versus the use of aspirin alone. **If cardioversion cannot be postponed for 3 weeks and the AF has been present for > 48 hours, patients should be anticoagulated (Table 24.2) with intravenous unfractionated heparin or subcutaneous low-molecular-weight heparin as a bridge to therapeutic INR or alternatively dabigatran, rivaroxaban or apixaban could be used and the patient should undergo transesophageal echocardiography (TEE) to rule out atrial thrombus; then anticoagulation should be used for at least 4 weeks after cardioversion.**

- b. A number of major trials have attempted to compare the benefits of aspirin and warfarin in minimizing the stroke risk in patients with AF. Overall, warfarin has shown an annual average reduction of 68% in relative risk for stroke, with aspirin showing a reduction anywhere from 0% to 44% (mean, ~30%). A recent trial has shown that clopidogrel reduces the risk of embolic stroke similar to that of aspirin and the combination of aspirin and clopidogrel is superior to either agent alone but inferior to warfarin therapy.

The decision to anticoagulate patients with AF depends on both the risk of thromboembolic complications and the risk of bleeding. In younger patients at low risk for stroke (younger than 65 years, without other risk factors), and who generally lead active lifestyles that place them at increased risk for bleeding, **aspirin** may be an acceptable alternative to warfarin. **Older patients at greater risk for stroke (age 65 and older, with or without other risk factors) should be anticoagulated with warfarin to maintain an INR of 2 to 3 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban. The risk of thromboembolism increases rapidly at INR levels even slightly < 2, and the risk of bleeding increases at INR levels > 3.** Studies of fixed low-dose warfarin and aspirin have shown ineffective protection from thromboembolic risk as compared with anticoagulation with warfarin to maintain an INR of 2 to 3, and thus are not recommended. **Patients who have contraindications to warfarin therapy should be treated with aspirin or the combination of aspirin and clopidogrel should be considered if the patients can tolerate it.**

TABLE 24.2 Anticoagulation Strategies in Patients Who Require Cardioversion

Length of time in atrial fibrillation	Elective cardioversion?	Timing and anticoagulation strategy
< 48 h	Yes	Depends on the presence of risk factors for thromboembolism
< 48 h	No	Immediate DCC may be performed without delay or need to start anticoagulation
> 48 h or unknown	Yes	A goal INR 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban for at least 3 weeks prior to and 4 weeks following DCC
> 48 h or unknown	Yes	A TEE can be performed while the patient is on IV heparin with a goal aPTT ratio of 1.5–2.0, and if no identifiable thrombus is present, DCC can safely be performed, followed by 4 weeks of oral coumadin with goal INR of 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban
> 48 h or unknown	Yes	If the TEE demonstrates a thrombus, then anticoagulation with coumadin with a goal INR of 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban for a period of 3 weeks prior to a repeat TEE to assess for thrombus resolution. If no identifiable thrombus is visible on repeat TEE, then DCC should be followed by at least 4 weeks of anticoagulation with INR of 2.0–3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban post DCC

DCC, direct current cardioversion; INR, international normalized ratio; TEE, transesophageal echocardiography; IV, intravenous.

The **risk of thromboembolism increases with longer duration of AF. Current guidelines recommend that patients who have been in AF for longer than 48 hours should be systemically anticoagulated** whenever possible. This can be accomplished quickly with intravenous unfractionated heparin, subcutaneous low-molecular-weight heparin, or oral dabigatran, rivaroxaban or apixaban. Cardioversion should be delayed in patients with AF of > 48 hours duration who have not been anticoagulated as described in the AHA guidelines discussed previously unless a patient is sufficiently unstable that more rapid cardioversion is necessary, in which case screening of the atria for the presence of thrombus with TEE is appropriate.

- c. TEE is highly effective in the detection of thrombus in the atria and in the left atrial appendage and is more sensitive in this regard than transthoracic echocardiography. The Assessment of Cardioversion using Transesophageal

Echocardiogram (ACUTE) study compared the use of TEE screening of patients with AF prior to cardioversion with a conventional approach based on 3 weeks of anticoagulation therapy. In the TEE group, those patients without thrombus on TEE underwent immediate cardioversion after therapeutic anticoagulation had been initiated and without waiting for 3 weeks. Patients were continued on warfarin for 4 weeks after the cardioversion as in the conventional group. No significant difference was noted in the embolic event rate or in the likelihood of maintenance of normal rhythm. TEE cardioversion is now considered an acceptable alternative when the conventional approach is not possible.

- d. Cardiac output may be decreased after cardioversion in up to one-third of patients, and this can persist for as long as a week. Rarely, this leads to pulmonary edema as soon as 3 hours after cardioversion. Atrial function also declines immediately after cardioversion, even after that occurring spontaneously or pharmacologically. Cardiac output should return to baseline within 4 weeks. The risk of thromboembolism is thus still increased during this time period, and that is why systemic anticoagulation is recommended for a minimum of 4 weeks after cardioversion.
 - e. After 4 weeks of therapy, the decision to continue anticoagulation is based on each patient's individual risk for recurrence of AF. **Patients who cannot be successfully cardioverted should be anticoagulated long-term**, as should patients with frequent recurrences/paroxysms.
 - f. In addition to the expanding number of pharmacologic options for anticoagulation, there are now nonpharmacologic methods for reducing thromboembolic risk. In the Embolic Protection in Patients with Atrial Fibrillation Trial (PROTECT trial), the WATCHMAN left atrial appendage occlusion system was noninferior to anticoagulation with warfarin in terms of thromboembolic outcomes. More data are needed on the long term safety and efficacy of this device.
3. **Rate control during AF.** Patients with AF may have controlled heart rates at rest, but they accelerate even with mild exercise. Hence, it is useful in patients with chronic AF to evaluate the heart rate response to submaximal or maximal exercise or to monitor the heart rate over an extended period (such as a 24-hour Holter monitor). The traditional criteria defining that adequate rate control varies with age but usually involves achieving a ventricular rate between 60 and 80 beats/min at rest and between 90 and 110 beats/min during moderate exercise have not been shown to be beneficial over a more lenient approach to achieve a resting heart rate of < 110 beats/min in patients with persistent or continuous AF and stable LV systolic function.
 4. **Restoration and maintenance of sinus rhythm.** There is debate whether restoration to sinus rhythm is beneficial for patients whose disease is asymptomatic as compared with a combined strategy of simply controlling the ventricular response and minimizing the thromboembolic risk. Data from nonrandomized trials show an increase in mortality in patients on long-term antiarrhythmic therapy for AF. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial compared two treatment strategies in patients with asymptomatic or tolerable AF. One group was treated with antiarrhythmic drugs and cardioversion as necessary to maintain sinus rhythm. The other group was allowed to remain in AF and the ventricular rate alone was controlled. Both groups received anticoagulation therapy. There was no difference in survival or embolic event rate between the two groups.
 - a. Direct current cardioversion. When restoration of sinus rhythm is deemed necessary, this is most effectively carried out with DCC. **DCC is successful at least 80% of the time**, whereas pharmacologic rates of successful cardioversion are lower and depend on the antiarrhythmic drug used and the clinical scenario. Whenever possible, **DCC should be carried out under sedation, with appropriate cardiac and hemodynamic monitoring, and**

in the presence of personnel skilled in airway control/management. See Chapter 59 for details of DCC, including sedation and methods.

b. Pharmacologic cardioversion

(1) The “drugs first” approach may promote more successful DCC and/or maintenance of sinus rhythm after DCC, if the attempt at pharmacologic cardioversion is unsuccessful. Similarly, it is reasonable to **attempt chemical cardioversion on any patient who fails DCC**, especially before repeated attempts at DCC.

(2) **Table 24.3 shows the currently available intravenous agents available** for the pharmacologic cardioversion of AF to sinus rhythm.

(i) Procainamide is a class IA antiarrhythmic drug that is often considered **the first line of therapy** for the pharmacologic conversion of AF occurring in the postoperative period after cardiac surgery.

TABLE 24.3 Intravenous Medications Used for the Cardioversion of Atrial Fibrillation

Drug name	Vaughan Williams class	Dose	Adverse side effects
Amiodarone	III	5–7 mg/kg over 30–60 min, followed by 1.2–1.8 g/d until 10 g, then 200–400 mg daily for maintenance	Hypotension, bradycardia, hyperthyroidism, hepatitis, skin discoloration, and phlebitis
Ibutilide	III	1 mg over 10 min, repeat as needed	Torsade de pointes, increased QTc
Propafenone	IC	1.5–2.0 mg/kg over 20 min	Hypotension and atrial flutter with RVR
Flecainide	IC	1.5–3.0 mg/kg over 10–20 min	Hypotension and atrial flutter with RVR
Vernakalant (approved in Europe but not yet in United States)	III	3 mg/kg IV infusion over 10 min. Second infusion of 2 mg/kg IV over 10 min after 15 min of rest	Vernakalant is contraindicated in patients with systolic blood pressure < 100 mm Hg, severe aortic stenosis, heart failure (NYHA classes III and IV), ACS within the previous 30 d, or QT interval prolongation. Before its use, the patients should be adequately hydrated. ECG and hemodynamic monitoring should be used, and the infusion can be followed by DCC if necessary. The drug is not contraindicated in patients with stable coronary artery disease, hypertensive heart disease, or mild heart failure

RVR, rapid ventricular response; ACS, acute coronary syndrome; ECG, electrocardiogram; DCC, direct current cardioversion.

- (ii) Amiodarone is considered a class III antiarrhythmic drug, although it has properties of all of the four Vaughan Williams classes. Like procainamide, amiodarone is commonly used intravenously in the postoperative period for AF after cardiac surgery, particularly for those patients with renal insufficiency or failure who are not candidates for procainamide.
 - (iii) Ibutilide is an agent approved for the pharmacologic conversion of AF. The incidence of torsade de pointes is at least 1% to 2% with ibutilide, which is higher than that seen with procainamide or amiodarone. Ibutilide is available only in the intravenous form and is, therefore, not an option for long-term maintenance of sinus rhythm.
 - (iv) Vernakalant is an agent that was recently approved in Europe for chemical cardioversion but has not yet been approved by the US Food and Drug Administration (FDA). It is more effective than amiodarone for conversion of AF to sinus rhythm. Vernakalant is contraindicated in patients with systolic blood pressure < 100 mm Hg, severe aortic stenosis, heart failure (NYHA classes III and IV), acute coronary syndrome (ACS) within the previous 30 days, or QT interval prolongation. Before its use, patients should be adequately hydrated. ECG and hemodynamic monitoring are mandatory, and the infusion can be followed by DCC if necessary. The drug is not contraindicated in patients with stable CAD, hypertensive heart disease, or mild heart failure. The clinical positioning of this drug has not yet been determined, but it is likely to be used for acute termination of recent-onset AF in patients with lone AF or AF associated with hypertension, CAD, or mild to moderate (NYHA classes I and II) heart failure.
- (3) A number of **oral agents** are available for the pharmacologic cardioversion of AF. **In appropriate patients the class IC agents, such as flecainide and propafenone, may be particularly effective for pharmacologic cardioversion.** In the text to follow are mentioned some other agents that may be used in the long-term for maintenance of sinus rhythm in patients with AF. It should be kept in mind that initiation or upward dose titration of antiarrhythmic drugs should be done with caution and, in many instances, should be performed in a hospital setting with a cardiac monitor. This is particularly true for the class III agents sotalol and dofetilide. On the other hand, in patients without structural heart disease, the class IC agents flecainide and propafenone may be considered for initiation on an outpatient basis. Table 24.4 outlines the presently available orally acting medications to treat AF.
- (i) **Class IA agents.** These agents have seen a decline in their use, primarily due to a high incidence of intolerance because of side effects but also due to evidence of possible increased mortality for those patients with structural heart disease.
 - **Procainamide.** This medication has not been used as frequently now for long-term treatment of AF, especially due to the potential for gastrointestinal, hematologic, and immunologic (e.g., lupus-like syndrome) side effects. An active metabolite of this drug, *n*-acetylprocainamide (NAPA), is cleared renally and has class III antiarrhythmic properties. Blood levels of both procainamide and NAPA need to be monitored to prevent toxicity, especially in the setting of renal and/or hepatic insufficiency.
 - **Quinidine** is another class IA drug that has not been used as frequently in recent years, again primarily due to a relatively high

TABLE 24.4 Oral Agents Available for Rhythm Control in Atrial Fibrillation

Drug name	Vaughan Williams class	Cardioversion dose		Daily maintenance dose
Amiodarone	III	400–800 tid dosing daily until 10 g, then		200–400 mg
Dofetilide	III	Based on CrCl (mL/min):	Dose: (µg bid)	Same. Dosing also adjusted for adjusted QTc
		> 60 mL/min	500	
		40–60	250	
		20–40	125	
		< 20	Contraindicated	
Propafenone	IC	600 mg		450–900 mg
Flecainide	IC	200–300 mg		Same
Sotalol	III	160–320 mg		Same
Dronedarone	III		Contraindicated if CrCl < 30 and patient with class IV heart failure, admission for CHF in preceding 4 weeks especially if EF < 35%	400 mg bid

CHF, congestive heart failure; EF, ejection fraction; IV, intravenous.

incidence of gastrointestinal, hematologic, and neurologic side effects. In addition, quinidine interacts with several cardiac and noncardiac medications.

- **Disopyramide.** This antiarrhythmic medication may have a “niche” for the treatment of vagally mediated AF or AF that occurs in the setting of hypertrophic cardiomyopathy. However, its **negative inotropic effects** are greater than those of other class IA drugs, and it is associated with **greater anticholinergic effects** such as constipation and urinary retention.
- (ii) **Class IC agents.** This group has become the preferred antiarrhythmic drugs for the management of AF in patients without structural heart disease, especially those patients with “lone” AF. These medications should not be used in patients with structural heart disease, especially patients with known or suspected ischemic heart disease. **Flecainide** was shown in the Cardiac Arrhythmia Suppression Trial (CAST) to be associated with increased mortality when used for suppression of ventricular arrhythmias in patients with LV dysfunction

following myocardial infarction (MI). This has led to much concern over the use of the class IC agents in any patient with CAD and even in other types of structural heart disease.

- **Flecainide.** This is a well-tolerated medication that has a low incidence of neurologic side effects. This medication is approved in both oral and intravenous forms for the acute cardioversion of AF. Randomized trials with this drug show that it converts 60% to 70% of patients with new-onset AF at 4 hours and close to 90% at 8 hours. Oral administration and intravenous administration were equally efficacious, but the average response to the intravenous loading is seen within 1 hour, whereas it is 3 hours with the oral loading dose.
 - **Propafenone.** This is also a well-tolerated medication. Its β -blocking properties limit its use in patients intolerant of such medications. Like sotalol, this property allows for its use as a single agent for AF suppression and ventricular rate control.
- (iii) **Class III agents.** This group has become the preferred treatment for AF in patients with structural heart disease.
- Sotalol also has β -blocking properties, which makes it useful as a **single-agent therapy** for AF suppression and ventricular rate control. However, these properties are also responsible for the intolerance seen with this drug and may contribute to exacerbation of heart failure in some patients. **The dose must be reduced with renal insufficiency.**
 - **Dofetilide.** This is the latest antiarrhythmic drug to be approved by the FDA for management of AF. This drug is generally well tolerated and has been shown to be safe for patients with structural heart disease, in particular those patients who have had an MI and those with CHF. **This drug has been associated with proarrhythmia, especially in the setting of renal dysfunction. The prescription of the drug is tightly controlled, and only those certified in its use may prescribe it.**
 - **Amiodarone.** This is a unique medication in that it has properties of all four Vaughan Williams classes. It is also unique with regard to its very long elimination half-life (up to 120 days). Amiodarone is effective for the management of AF but is generally reserved for patients in whom other antiarrhythmic drugs have been ineffective or poorly tolerated, due to the important potential organ toxicities that may occur, predominantly in the liver, lungs, thyroid, and eyes. It is recommended that patients treated with amiodarone have baseline and then regular screening tests such as ophthalmologic examination, pulmonary function study, chest x-ray, and blood tests for liver and thyroid function.
 - **Dronedarone** is a multichannel blocker that inhibits the sodium, potassium, and calcium channels and has noncompetitive antiadrenergic activity. It is **similar to amiodarone with a much better side-effect profile, though it is less effective than amiodarone.** Contraindicated in NYHA classes III and IV or unstable heart failure, during concomitant therapy with QT-prolonging drugs, powerful CYP3A4 inhibitors, and creatinine clearance < 30 mg/mL. There is potential for serious liver toxicity with dronedarone and liver function tests have to be monitored closely when patients are on this medication.
 - **Azimilide.** New class III antiarrhythmic drug that is not yet FDA approved for the management of AF.

- (4) Figure 24.1, adapted from American Heart Association/American College of Cardiology/European Society of Cardiology (AHA/ACC/ESC) guidelines, outlines strategies used in the maintenance of sinus rhythm.

c. AV nodal ablation in conjunction with permanent pacemaker.

- (1) Symptomatic refractory AF, especially when the ventricular rate is uncontrollable or such control is limited by underlying bradycardia, may be amenable to ablation of the AV node and implantation of a **rate-responsive single-chamber permanent pacemaker**. These patients still require systemic anticoagulation. A recent meta-analysis of 21 studies that included 1,100 patients who underwent AV nodal ablation for highly symptomatic AF concluded that AV nodal ablation and subsequent pacemaker implantation significantly improved the quality of life, exercise capacity, and LV function and decreased symptoms of AF. In a small subset of 56 patients who had impaired LV function (an ejection fraction < 40%) and AV nodal ablation, permanent pacemaker implantation caused an average improvement in ejection fraction of 8% and complete normalization of the ejection fraction in one-third of the patients. The remaining patients with persistent LV dysfunction after AV nodal ablation had a 5-year survival rate of <40%. The 1-year mortality rate after AV nodal ablation and permanent pacemaker implantation is approximately 6.3%, which includes a high 2% risk of sudden cardiac death (SCD), which is thought to be related to early post pacemaker implantation R-on-T phenomenon caused by pacemaker-induced bradycardia. For this reason, it has been suggested, without a great deal of support in the published literature, that pacemakers be programmed with a minimum heart rate of 90 beats/min for the first month after the AV nodal ablation procedure.
- (2) **Indications for permanent pacemaker for AF.** A permanent pacemaker may be needed in patients who develop symptomatic bradycardia, which may be exacerbated by therapy for AF. This may occur because of an underlying sinus node dysfunction or perhaps poor AV conduction leading to slow ventricular rates during AF. Modern pacemakers have “**mode switching**” capabilities, so that the pacing mode changes from dual-chamber to single-chamber ventricular pacing at the onset of AF to avoid rapid ventricular pacing rates due to the pacemaker responding to the atrial activity.
- (3) **Limitations.** Although, as mentioned earlier, AV nodal ablation has been shown to cause symptomatic improvement in patients with refractory and very symptomatic AF, its limitations include the potential lifelong need for anticoagulation, the loss of AV synchrony, and the lifelong pacemaker dependence with its attendant risks.

Several recent pacemaker trials have shown worsening hemodynamic effects of right ventricular (RV) apical pacing compared with biventricular pacing. The Post AV Nodal Ablation Evaluation (PAVE) trial randomized patients to RV apical pacing versus biventricular pacing following AV nodal ablation for permanent AF. At an average follow-up of 6 months, the biventricular-paced group had longer 6-minute walk times and increased peak oxygen consumption and reported improved quality of life. Although LV ejection fraction did not differ between the groups at baseline, at follow-up, the ejection fraction in the biventricular pacing group stabilized, whereas the ejection fraction in the RV apically paced group had declined significantly.

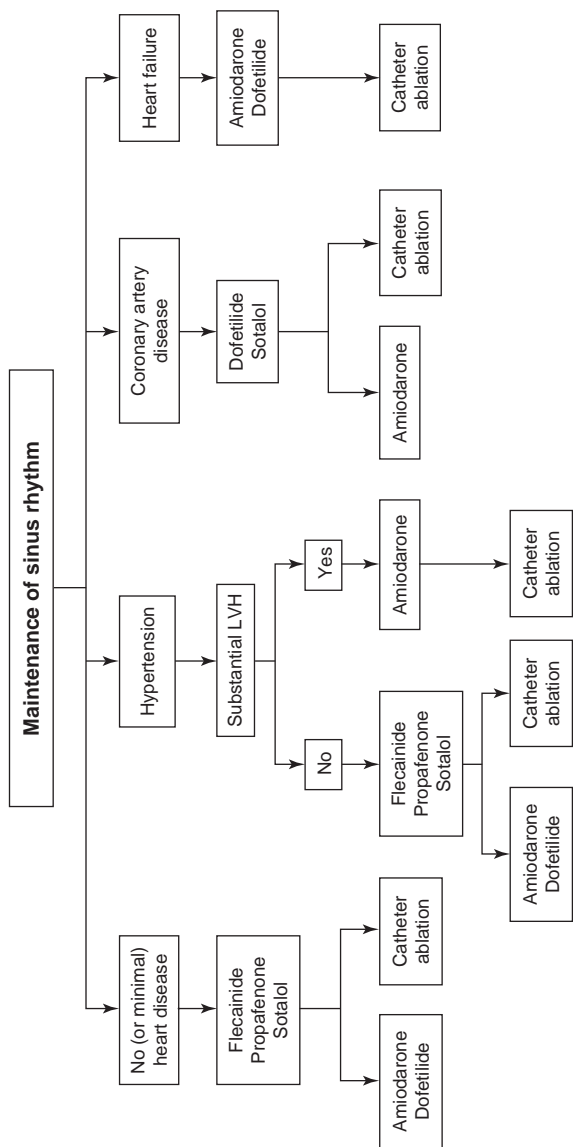


FIGURE 24.1 Therapeutic approach to the maintenance of sinus rhythm. Adapted from American College of Cardiology/American Heart Association (ACC/AHA) practice guidelines. LVH, left ventricular hypertrophy.

Current recommendations regarding the choice of pacemaker following AV nodal ablation suggest the use of RV pacing devices in patients with normal LV function or in those thought to have reversible LV dysfunction secondary to AF with poor rate control. In patients with impaired LV function not caused by AF, a biventricular pacemaker with or without defibrillator capability should be considered. In patients who have undergone AV nodal ablation and developed heart failure symptoms following RV apical pacing, an upgrade from an RV apical system to biventricular system should be considered.

- d. **Implantable devices** with treatment and suppressive strategies for AF are now available for selected patients. Some devices may terminate AF with a rapid atrial burst pacing or a cardioversion shock. Pacemakers that have pacing algorithms aimed at preventing AF episodes have become available. The use of such pacemakers in patients without an indication for pacing is still under investigation. A difficulty in their implementation is the frequency of episodes of AF in patients requiring device activation and the discomfort associated with shock delivery.
- e. **Invasive curative therapies.** There are two major interventional approaches for the management or cure of AF, one based on a percutaneous approach and the other on a surgical approach. These approaches are not yet first-line therapy, but in recent years have become a much more attractive option for patients with troublesome AF in whom antiarrhythmic treatment has been ineffective or poorly tolerated.

- (1) **Catheter ablation of AF with pulmonary vein isolation (PVI).** In 1998, Haissaguerre and colleagues described the presence of isolated foci in the left atrium and pulmonary veins and their role in the initiation of AF. They were also able to demonstrate that ablation of these foci could successfully terminate AF. Based on this early work, the field of AF ablation was born. Initial experiences with AF ablation attempted to mimic the surgical Maze procedure. Since that time, ablation has undergone various changes in both philosophy and technique.

Approaches to AF ablation can vary widely. Purely anatomic approaches may focus on the creation of linear lesions around the pulmonary veins and may not require demonstration of entrance or exit block. Other techniques focus on ablation of sites of autonomic ganglia or areas of complex fractionated electrograms. Electrogram-based approaches make use of a mapping catheter to help identify electrograms in areas targeted for isolation but may vary in the scope of the area targeted for isolation. Anatomic ablation techniques use recently developed three-dimensional (3D) mapping systems to demonstrate the anatomy of the left atrium and the pulmonary veins. Various anatomic techniques including the isolation of each of the four veins, individually or via isolation of two veins at a time, have been developed. In addition, anatomic lines extended to the mitral isthmus or involving the roof of the left atrium have been utilized. Exit block is often used as an end point in the anatomic approach.

Electrogram-based techniques require the use of a second (ring) mapping catheter. After circumferential isolation, the mapping catheter is used to evaluate for the presence of gaps in the ablation line and these gaps are then ablated. There have also been experiences using electrogram-based approaches to perform additional ablation points in other areas of the heart, including the coronary sinus, the superior vena cava, and the right atrium, after performing PVI. Additionally, drug testing with adenosine and isoproterenol to provoke AF and thereby identify potential triggers for ablation is sometimes used.

Advances in techniques have improved the efficacy and safety of the procedure. One major advance has been the development of protocols that ablate outside the ostia of the pulmonary veins to help reduce the incidence of postprocedure pulmonary vein stenosis. Catheter ablation is now considered a reasonable alternative to pharmacologic therapy to prevent recurrent AF in symptomatic patients with little or no left atrium enlargement with a class I recommendation in the most recent guideline update. In addition, catheter ablation performed in experienced centers is useful in maintaining sinus rhythm in selected patients with significantly symptomatic, paroxysmal AF who have failed treatment with an antiarrhythmic drug and have normal or mildly dilated left atria, normal or mildly reduced LV function, and no severe pulmonary disease.

Patient preparation and procedural considerations. Prior to ablation, considerations including access, conscious sedation, and choice of anticoagulation regimen should be made on an individual patient basis. The presence of multiple catheters in the left atrium requires patients to be given full anticoagulation. Prior to the procedure, some centers require patients to be therapeutic on warfarin for 4 to 6 weeks. Patients not anticoagulated prior to the procedure should undergo transesophageal echocardiogram to exclude the presence of left atrial thrombus. Regardless of preprocedural anticoagulation status, patients are fully anticoagulated with unfractionated heparin during the procedure to achieve a prespecified targeted activated clotting time.

Catheters are placed in the right atrium and coronary sinus, typically via sheaths in the right and left femoral veins, and an additional sheath is often needed if intracardiac echo is used. The left atrium is accessed via transeptal puncture. Great care is needed, using fluoroscopic guidance to assure successful transeptal puncture, and many centers use intracardiac echo to assist in safely achieving transeptal puncture. After placement in the left atrium, circular “lasso” mapping and ablation catheters are used to approach the pulmonary veins. If used, intracardiac echo can assist 3D mapping techniques in identifying the pulmonary vein ostia.

End point for ablation differs depending on the technique used. On completion of electrogram-based ablation, success is demonstrated by the development of entry block in the antrum of the pulmonary veins. However, anatomic-based procedures do not require the demonstration of block.

Centers performing ablation should have backup available of physicians experienced in pericardiocentesis and cardiothoracic surgery, secondary to the development of hemorrhagic pericardial effusion or atrial appendage rupture.

The identification of the pulmonary veins as the predominant source of ectopic foci that trigger AF has led to catheter-based ablation strategies to electrically isolate the pulmonary veins by delivering radiofrequency energy at their ostium. In the initial series, foci of increased automaticity within the pulmonary veins were targeted and ablated. In one early series of 45 patients with AF, 62% became free of symptomatic AF over a mean follow-up of 8 months. However 70% of the patients required multiple procedures. In a subsequent study using the same approach, the success rate (defined as the absence of return of symptomatic AF) was 86% over a 6-month follow-up.

Continued research into the substrate for AF has demonstrated that there are many potentials that can contribute to the initiation and maintenance of AF and that these may arise in multiple areas of the right and left atria. Thus, catheter ablation procedures have been developed to

incorporate linear lesions in the roof of the left atrium and mitral valve isthmus ablation to account for these. Using this approach in a series of 70 patients with symptomatic AF, 70% of the patients were found to be free from AF following PVI without antiarrhythmic medications at 4 months of follow-up. The procedure continued to advance with the development of the circular mapping catheter, which allowed for more accurate mapping and isolation of the pulmonary veins.

At the time of this writing, the accumulated published experience in PVI suggests an approximately 70% to 90% success rate in patients with paroxysmal AF and 40% to 80% success rate in patients with persistent AF. It must be noted that the success rates in patients with depressed ejection fraction are much lower than that in patients with normal systolic function.

A newer approach to radiofrequency catheter ablation of AF involves the ablation of complex fractionated electrograms, which has a 91% efficacy reported at 1 year. This study also showed that restoration of sinus rhythm following catheter-based ablation of AF caused a significant improvement in exercise capacity, quality of life, and LV systolic function.

Presently, the long-term efficacy of catheter-based ablation is not known and requires further study. Long-term follow-ups from RCTs are presently either lacking in patient numbers or marred by high crossover rates or by antiarrhythmic use. The current ACC/AHA/HRS guidelines allow for the use of PVI in the treatment of symptomatic AF following intolerance to, depending on the substrate, at least one drug and as many as three antiarrhythmic drugs.

Complications. Major complications from catheter-based ablation have been reported in about 2% to 3% of patients and include pulmonary vein stenosis, systemic thromboembolism, atrial esophageal fistula, and the development of atypical left atrial flutter.

The incidence of **pulmonary vein stenosis** has diminished by the judicious use of radiofrequency ablation energy to target areas just outside the pulmonary veins so as to isolate the ostia of the pulmonary veins from the remainder of the left atrium. The use of intracardiac echocardiography to detect microbubble formation as a means to measure the magnitude of radiofrequency energy delivered has been reported to reduce the instance of pulmonary vein stenosis. This complication often presents as dyspnea and breathlessness in the weeks to months following catheter-based ablation, with radiographic evidence of asymmetric pulmonary edema or pulmonary emboli, as it results in obstructive venous outflow from a single pulmonary lobe. This diagnosis is best made by the use of computed tomography venography, but it can also be made through the use of TEE with the finding of high-velocity flow in the affected pulmonary vein.

Systemic embolic events, including embolic stroke, are among the most serious complications of catheter-based ablation of AF, and the reported incidence varies from 0% to 5%. A trial comparing heparin-dosing regimens found that increasing the intensity of anticoagulation reduces the probability of forming left atrial thrombi from 11% to 3%, when the activated clotting time was increased from 250 to > 300 seconds.

Atrial esophageal fistula is a relatively rare complication of PVI, and it is more likely to occur when extensive ablation occurs over the posterior left atrial wall where it abuts the esophagus. Typical symptoms include nausea, vomiting, fever, and sudden neurologic deterioration

(from systemic embolization), which occur in the days to weeks following ablation. Successful treatment of this condition requires prompt recognition of its clinical signs, as delay in the treatment often leads to death.

The development of **atypical left atrial flutter** is thought to be related to the development of scar in the left atrium, which creates the substrate for reentry required for this arrhythmia. The most important predictor of the development of left atrial flutter is the presence of an incomplete line of ablation, and it has been found that extending the ablation line to the mitral valve annulus may reduce the frequency of this complication. This arrhythmia, as is the case with right atrial flutter, is amenable to further catheter-based ablation.

- (2) Cox-Maze procedure is a surgical approach that has been developed over the last 25 years and that tested the original hypothesis that reentry is the predominant mechanism for the development and maintenance of AF. It has undergone multiple revisions through the years, and now it has evolved to include techniques that surgically isolate the pulmonary veins and connect these dividing lines to the mitral valve annulus. The surgical procedure uses atrial incisions in critical locations to create barriers to the propagating wavelets that are responsible for the initiation and maintenance of AF and that consequently eliminate the macroreentrant circuits in the atrium necessary to maintain AF.

The Maze procedure has changed over the last two decades, and present techniques use transmural lesions to isolate the pulmonary veins and to connect these dividing lines to the mitral valve annulus, as well as lesions to create barriers in the right atrium. The reported success of the combined three developmental stages of the Cox-Maze procedure is 93% in patients with symptomatic AF who were intolerant of antiarrhythmic drugs. This long-term report included 178 patients, and there was a 2.2% risk of periprocedure death and a 6% risk of pacemaker requirement in the patients undergoing a Cox-Maze I procedure. Other, more current studies have reported lower success rate of around 70%. This procedure maintains the atrial transport function, and especially when allied with left atrial appendage ligation substantially reduces the risk of postoperative thromboembolic events.

Procedure risks include **death** risk, which is dependent on the patient's comorbidities but is usually estimated to be < 1% as an isolated procedure, the need for a **pacemaker, impaired atrial transport function**, and delayed **atrial arrhythmias** including atrial flutter.

The Maze procedure has not had widespread acceptance as a means of treatment for AF, except in patients undergoing open heart surgery. Even in these patients, the additional intraoperative time and complexity of the procedure have limited its widespread surgical application. Currently under development are less invasive approaches, including thoracoscopic and catheter-based epicardial techniques.

The Maze procedure is often associated with significant edema formation, probably due to atrial natriuretic peptide derangements. This is effectively mitigated by the use of aldosterone antagonists such as spironolactone for the first 4 to 6 weeks postoperatively. All procedures used to restore NSR in patients with AF have had a variable effect on the restoration of atrial transport function, depending on the duration of fibrillation before the procedure and the rhythm maintained following the procedure. The need for long-term anticoagulation therapy following these procedures is generally assessed on an individual basis.

II. SPECIAL CONSIDERATIONS

A. Postoperative AF. AF is common postoperatively. The incidence of AF postoperatively varies with the type of surgery and is highest following open heart surgery, during which time it ranges between 20% and 50%. It usually occurs in the first 5 days. Risk factors for perioperative AF include age, a history of AF, chronic obstructive pulmonary disease (COPD), valvular heart disease (especially mitral valve disease), atrial enlargement, perioperative heart failure, and withdrawal from a β -blocker or an ACE inhibitor. Postoperative AF is a major determinant of length of stay and thus of cost. It is associated with all the risks associated with AF in the non-postoperative setting including hemodynamic compromise and thromboembolism.

1. Therapy. Postoperative AF is usually self-limited, and DCC is usually not needed. There are a variety of antiarrhythmic agents available for cardioversion in postoperative patients. In a small trial, ibutilide was found to be more effective than placebo for the treatment of postoperative AF. Sotalol is particularly acutely effective in patients with preserved LV systolic function, because the risk of proarrhythmic toxicity is small and also because its β -blocker action contributes to slowing the ventricular rate.

AF carries an increased risk of stroke in post-CABG patients, and so anticoagulation with heparin followed by oral anticoagulants is recommended if AF persists for longer than 48 hours. The choice of antiarrhythmic therapy, choice of AV nodal blocking agents, and the use of either heparin and/or oral anticoagulants depend on the individual patient, the time from surgery, and the specific type of surgery.

2. Prevention. There is evidence supporting the prophylactic administration of β -blocker medications in patients undergoing cardiac surgery to prevent the development of AF. Sotalol has also been studied, but there is at present conflicting evidence regarding its effectiveness. Amiodarone, when given either prophylactically before cardiac surgery or following open heart surgery, has been found to significantly reduce the incidence of postoperative AF. In the Prophylactic Oral Amiodarone for the Prevention of Arrhythmias that Began Early After Revascularization (PAPABEAR) trial, oral amiodarone, dosed at 10 mg/kg beginning 6 days before and continuing for 6 days after surgery, decreased the incidence of postoperative AF by 50%. This efficacy was present in patients irrespective of whether CABG, valve surgery, or a combination was performed. Preoperative treatment with procainamide has yielded inconsistent results, as has treatment with either digoxin or verapamil.

At present there are limited data supporting the use of atrial overdrive pacing as opposed to single-chamber pacing in the prevention of postoperative AF. In a randomized trial involving 132 patients undergoing CABG, postoperative biatrial pacing significantly reduced incidence of AF by 12.5% compared with left atrial pacing, right atrial pacing, or no pacing. A meta-analysis of 10 randomized trials also concluded that biatrial pacing, atrial pacing, and right atrial pacing reduced the incidence of AF after CABG surgery.

B. AF in acute MI. The incidence of AF following acute MI varies depending on the population sampled as well as the type of MI but ranges between 10% and 20% at 30 days. AF is more commonly associated with acute MI in older patients as well as those with a higher Killip class and more severe LV dysfunction. Patients with AF in the setting of an acute MI have a worse outcome at 30 days than those in sinus rhythm (29.3% with AF vs. 19% with NSR). Stroke rates are also increased in patients with post-MI AF.

The guidelines presently recommend urgent DCC in patients with acute MI who present with AF, especially if in rapid ventricular response with intractable ischemia or evidence of hemodynamic instability including CHF. Intravenous β -blockade is indicated for rate control to reduce myocardial oxygen consumption and demand, and digoxin is an alternative in patients with severe left surgical dysfunction and

heart failure. Anticoagulation is recommended in patients with large anterior MIs and those in which the AF becomes persistent. Post-MI ACE inhibitors seem to reduce the incidence of AF in patients with significant LV dysfunction. Post-MI use of carvedilol also seems to diminish the incidence of AF and atrial flutter.

- C. AF and WPW syndrome.** The most feared complication of the WPW syndrome is the development of ventricular fibrillation and SCD secondary to antegrade conduction of the AF into the ventricles. The incidence of SCD in patients with a WPW syndrome is around 0.6% per year, and risk factors for SCD include having a short antegrade bypass tract refractory period (< 250 milliseconds), short RR intervals during preexcited AF, and the presence of multiple accessory pathways.

It is important to avoid AV nodal blocking agents in a patient who presents with a preexcited tachycardia, as this has the potential to increase the refractory period of the AV node and facilitate conduction down the accessory pathway. Administration of AV nodal blocking agents such as verapamil, diltiazem, and digoxin is contraindicated in this setting. Intravenous β -blockers are ineffective in this setting and may have adverse hemodynamic consequences.

Flecainide, a class IC antiarrhythmic agent, can be used to slow the ventricular rate in patients who have AF with rapid ventricular rates associated with preexcitation by shortening the shortest preexcited cycle length during AF.

Patients with WPW syndrome and syncope or with a short antegrade bypass tract refractory period require immediate DCC followed by catheter-based ablation of the accessory pathway as the preferred therapy. Ablation of the bypass tract does not necessarily prevent recurrence of the AF, but it should be noted that following this ablation the management of AF is similar to that of patients without preexcitation.

- D. AF in pregnancy.** AF occurs infrequently during pregnancy and when it does it usually has an identifiable cause, such as mitral valve disease, thyroid disease, or pulmonary processes. The ventricular rate can be controlled with digoxin, β -blockers, or a nondihydropyridine calcium channel blocker. Currently available antiarrhythmic medications cross the placenta and are excreted in breast milk and should be avoided if possible in the pregnant and lactating individuals, but amiodarone, sotalol, and flecainide have all been used successfully during pregnancy in selected instances. Quinidine has the longest safety record of any antiarrhythmic agent in pregnancy and remains the agent of choice for pharmacologic conversion of AF. In the hemodynamically unstable patient, DCC can be performed without any concerns of fetal damage.

Anticoagulation should also be given high priority during pregnancy, given the risk of thromboembolic disease during pregnancy, and only those patients with lone AF at low risk for thromboembolic complications do not require anticoagulants.

The oral anticoagulant warfarin is generally avoided during the first trimester of pregnancy because of teratogenic effects and also during the last month of pregnancy because of bleeding concerns during delivery. Administration of unfractionated heparin either by continuous intravenous infusion in a dose sufficient to increase the activated partial thromboplastin time (aPTT) to 1.5 to 2 times control or by intermittent subcutaneous injection of 10,000 to 20,000 units every 12 hours adjusted to prolong the midinterval aPTT to 1.5 times control is appropriate. Low-molecular-weight heparin may also be considered during the first trimester and last month of pregnancy, although there are limited data on clinical outcomes with its use.

- E. AF and hypertrophic obstructive cardiomyopathy (HOCM).** Patients with AF and HOCM have a high risk of systemic embolic events. For this reason, it is recommended to maintain oral anticoagulation therapy in the range of an INR of 2.0 to 3.0 or alternative anticoagulation with dabigatran, rivaroxaban or apixaban in patients with HOCM and AF regardless of what the CHADS₂ score is. Antiarrhythmic medications can be used to prevent recurrent episodes of AF, and although there are insufficient data comparing the various antiarrhythmics, anecdotal evidence seems to support the use of disopyramide in combination with a β -blocker or a nondihydropyridine calcium channel blocker.

F. AF and pulmonary disease. AF commonly develops in patients with COPD exacerbations. General recommendations include the treatment of the underlying lung process, correction of hypoxia, and of the acid–base imbalances. Medications commonly used to treat bronchospastic airway disease such as theophylline and β -adrenergic agonists can precipitate AF and decrease the ability of medications to control the ventricular rate. Antiarrhythmic medications with β -blocking properties such as sotalol, propafenone, and adenosine can worsen bronchospasm and are contraindicated in patients with severe bronchospastic airway disease. Ventricular rate control is usually achieved with nondihydropyridine calcium channel blockers such as verapamil and diltiazem.

ACKNOWLEDGMENTS: *The authors acknowledge the contribution of Dr. Carlos Alves to an earlier edition of this chapter.*

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SECTION

V

Vascular and Pericardial Disease

EDITOR

Esther S.H. Kim

Venous Thromboembolism and Hypercoagulable States

I. VENOUS THROMBOEMBOLISM AND HYPERCOAGULABLE STATES

A. Venous thromboembolism (VTE). Deep vein thrombosis (DVT) and pulmonary embolism (PE) represent different manifestations of the same clinical entity referred to as venous thromboembolism (VTE). It is a common, lethal disease that affects hospitalized and nonhospitalized patients, recurs frequently, is often overlooked, and can result in long-term complications, including chronic thromboembolic pulmonary hypertension (CTPH) and the postthrombotic syndrome (PTS). Although PE is the third most common cause of hospital-related death in the United States, less than half of all hospitalized patients at risk for VTE receive adequate prophylactic treatment. Most hospitalized patients have at least one or more risk factors for VTE, and **without prophylaxis, the incidence of hospital-acquired DVT is 10% to 20% among medical patients and even higher among surgical patients (15% to 40%).**

- 1. Deep vein thrombosis.** The lower extremities are the most common sites for DVT, but other affected sites include the upper extremities and the mesenteric and pelvic veins. The main goal in the management of DVT is the prevention of PE and PTS. Proximal lower extremity DVTs (popliteal vein and above) have an estimated risk of PE of 50% if not treated. Approximately 25% of calf vein thrombi propagate (in the absence of treatment) to involve the popliteal vein or above.
- 2. Pathogenesis and risk factors.** Virchow's triad still forms the best framework for understanding the pathogenesis of VTE. **The triad includes stasis, hypercoagulability, and injury to the vessel wall.** There are both inherited and acquired risk factors for hypercoagulability. The most common **inherited** risk factors include **factor V Leiden (FVL)** and **prothrombin gene mutation (G20210A)**; deficiency of the natural **anticoagulant protein C (PC), protein S (PS)**, and **antithrombin (AT)**; **hyperhomocysteinemia**; and **elevated factor VIII** levels. Acquired risk factors include **immobilization, surgery, trauma, pregnancy**, use of oral **contraceptives (OCPs)** or **hormone replacement therapy (HRT)**, **malignancy**, **antiphospholipid syndrome** (lupus anticoagulant and/or anticardiolipin antibodies), **heparin-induced thrombocytopenia (HIT)**, **myeloproliferative disorders**, **smoking, obesity** (body mass index [BMI] > 30), **inflammatory bowel disease**, **central venous catheters** or **pacemakers**, and **the nephrotic syndrome**.
- 3. Clinical manifestations.** Typical symptoms of DVT in the upper and lower extremities include pain and swelling. Signs of DVT on physical examination may include increased warmth, tenderness, edema, the presence of dilated veins (collaterals), erythema, and, in extreme situations, cyanosis or gangrene. Various signs such as Homans' sign (dorsiflexion of the ankle with the knee at 30° flexion causing calf pain), Louvel's sign (worsening of pain with coughing or sneezing), and Lowenberg's sign (more pain on the affected leg after inflation of a sphygmomanometer around each calf) have been described, but these are

neither sensitive nor specific for the diagnosis. A limb-threatening manifestation of DVT, **phlegmasia cerulea dolens**, occurs most often in the setting of malignancy, HIT, or other hypercoagulable conditions in which the thrombus completely occludes venous outflow, causing massive limb swelling, hypertension in the capillary bed, and eventually ischemia and necrosis. Phlegmasia cerulea dolens is a vascular emergency requiring leg elevation, anticoagulation, and, in select cases, thrombolysis or surgical or catheter-based thrombectomy. Fasciotomy may also be required to relieve associated compartmental syndromes.

4. Diagnosis

a. **Clinical examination** is unreliable in the diagnosis of DVT, as symptoms and signs are often insensitive and nonspecific. Pretest probability scores improve the utility of further testing. For example, using the Wells score (Table 25.1), patients in the low pretest probability category have a 96% negative predictive value for DVT (99% if the D-dimer is negative as well), but the positive predictive value in patients with a high pretest probability is < 75%, supporting the need for further diagnostic testing to identify patients with thrombosis.

TABLE 25.1 Pretest Probability of Deep Vein Thrombosis (Wells Score)

Clinical feature ^a	Score
Active cancer (treatment ongoing or within previous 6 mo of palliative treatment)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for more than 3 d or major surgery, within 4 wk	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling by more than 3 cm when compared with the asymptomatic leg (measured 10 cm below tibial tuberosity)	1
Pitting edema (greater in the symptomatic leg)	1
Collateral superficial veins (nonvaricose)	1
Alternative diagnosis as likely or greater than that of DVT	-2
Score	
High	3 or greater
Moderate	1 or 2
Low	0 or less
Modified score (adds one point if there is a previously documented DVT)	
Likely	2 or more
Unlikely	1 or less

DVT, deep vein thrombosis.

^aIn patients with symptoms in both legs, the more symptomatic leg is used.

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- b. **Venography** has been the gold standard test for the diagnosis of DVT in the past. The presence of an intraluminal filling defect is diagnostic, although abrupt cutoffs, nonfilling of the deep venous system, and/or demonstration of collateral flow may also serve as evidence for the presence of DVT. However, because venography is invasive and requires the use of potentially harmful contrast agents, it has largely been replaced by noninvasive tests such as duplex ultrasonography.
- c. **Duplex ultrasonography** has a sensitivity and specificity of about 95% and 98%, respectively, for the detection of proximal DVT in symptomatic patients; however, it is operator dependent and is less sensitive in asymptomatic individuals and for thrombi located in the calf veins. **An inability to compress the vein with the ultrasound transducer is diagnostic for DVT.** Other findings suggestive, but not diagnostic, of an acute DVT include venous distention or absent or decreased spontaneous flow. Diagnosis of recurrent DVT is more challenging, given the high incidence of persistently noncompressible veins after an initial event. Other limitations of compression ultrasonography include difficulty in detecting isolated thrombi in the iliac veins or femoral veins within the abductor canal. False positives may occur when pelvic masses result in isolated noncompressibility of the common femoral veins.
- d. **D-Dimer.** The sensitivity and negative predictive value of this test are high. The combination of a **low pretest probability and a negative D-dimer has an extremely high negative predictive value for VTE (approximately 99%).** A positive D-dimer, however, is nonspecific, and other diagnostic testing should be performed.
- e. Other diagnostic tests less frequently used to detect DVT include magnetic resonance venous imaging and computed tomography (CT). These tests are mainly helpful in the diagnosis of DVT in the pelvic veins, inferior vena cava (IVC), or mesenteric veins.

5. Treatment

- a. The main goals of treatment for DVT include relief of symptoms and prevention of PE, CTPH, PTS, and recurrent VTE. Once the diagnosis of DVT is confirmed, **anticoagulation should be started immediately unless there is a contraindication.** Initial therapy should include heparin, low-molecular-weight heparin (LMWH), or fondaparinux followed by an oral anticoagulant (vitamin K antagonist or VKA). LMWH and fondaparinux are renally cleared, and although the LMWHs can be given in patients with renal insufficiency after dose adjustment, both are contraindicated in patients requiring dialysis.

Weight-based dosing of unfractionated heparin (UFH) (80 U/kg bolus followed by 18 U/kg/h intravenous [IV] infusion) has been shown to achieve a therapeutic activated partial thromboplastin time (aPTT) more rapidly than fixed-dose regimens. The target aPTT has traditionally been 1.5 to 2.5 times the control aPTT; however, the actual therapeutic aPTT range varies among laboratories because of their use of different aPTT reagents. The American College of Chest Physicians (ACCP) and the College of American Pathologists now advocate the use of an anti-factor Xa assay to establish a heparin dose-response curve for the aPTT ratio (of each laboratory), using concentrations that correlate to therapeutic heparin levels of 0.3 to 0.7 IU/mL determined by factor Xa inhibition. The aPTT should not be followed in patients with an abnormal baseline aPTT (e.g., in patients with lupus anticoagulant) and in patients who require unusually high doses of heparin such as in AT deficiency. In these situations, the anti-factor Xa assay should be used. UFH can also be administered subcutaneously as an alternative to IV administration, and several dosing nomograms have been recommended. One approach is to give an initial IV bolus of 5,000 U followed by a subcutaneous dose of 17,500 U twice daily on the first day. Blood for an aPTT is drawn 6 hours after

the initiation dose, and subsequent doses are adjusted accordingly to achieve an aPTT 1.5 to 2.5 times the control. Another fixed-dose nomogram recommends a subcutaneous loading dose of 333 U/kg followed by fixed doses of 250 U/kg subcutaneously every 12 hours without the need for aPTT monitoring.

LMWH is administered as a weight-based subcutaneous injection. Enoxaparin, the most commonly used agent in the United States, is given either as a once-daily injection (1.5 mg/kg/d) or twice per day (1 mg/kg every 12 hours). No monitoring is required except in obese, pediatric, or pregnant patients or patients with renal insufficiency. The anti-Xa level using LMWH as a reference standard should be measured 4 hours after an injection. The therapeutic range is 0.5 to 1.0 IU/mL for the 12-hour regimen and ≥ 1.0 IU/mL for the daily dose.

Once anticoagulation with UFH or LMWH is begun, a VKA may be initiated. The overlap should be continued for a minimum of 4 to 5 days and until the international normalized ratio (INR) is within the target range of 2.0 to 3.0 for two consecutive days to permit adequate depletion of vitamin K–dependent coagulation factors.

Fondaparinux, an indirect factor Xa inhibitor, is approved by the US Food and Drug Administration (FDA) for use as DVT prophylaxis in patients undergoing orthopedic procedures (total hip and knee arthroplasty) and abdominal surgery. It is also approved as treatment for acute DVT and PE when used in combination with a VKA. Its efficacy and safety in comparison with LMWH for the treatment of acute DVT and in comparison with IV UFH for the treatment of PE have been shown in large randomized controlled trials. Fondaparinux is administered as a once-daily subcutaneous injection of 2.5 mg for DVT prophylaxis and 5, 7.5, or 10 mg based on body weight (< 50 , 50 to 100, and > 100 kg, respectively) for the treatment of DVT or PE. Fondaparinux is contraindicated in patients with severe renal impairment (creatinine clearance < 30 mL/min) and bacterial endocarditis. When used as DVT prophylaxis, fondaparinux is also contraindicated in patients with body weight < 50 kg who are undergoing hip fracture, hip replacement or knee replacement surgery, and abdominal surgery.

Thrombolytic therapy for DVT may be beneficial in select individuals and is preferably administered locally via a catheter-directed approach. Systemic lysis is also an option if a catheter-directed approach is not available. Both routes carry an increased risk of systemic hemorrhage compared with standard anticoagulation alone. Although it has been suggested that the use of thrombolytics promotes early recanalization and minimizes the incidence of PTS, their role in DVT treatment in the absence of a threatened limb is still unclear. The current ACCP guidelines recommend against their routine use in patients with DVT, except for those patients (without contraindication) with an extensive acute proximal DVT (ileofemoral DVT) or individuals at risk for limb gangrene secondary to venous occlusion.

Damage to the venous valves from lower extremity DVT and venous hypertension can lead to the development of PTS, a condition characterized by leg edema, skin changes such as hyperpigmentation and lipodermatosclerosis, pain, and, in severe cases, stasis ulceration. The incidence of this complication is drastically reduced with the use of **compression stockings**, and current guidelines recommend the use of stockings at a pressure of 30 to 40 mm Hg at the ankle for 2 years after an episode of DVT. In addition, early ambulation as tolerated after diagnosis is encouraged, as mobile patients with DVT do not require bed rest.

- b. **Vena caval interruption.** Current guidelines recommend against the routine insertion of IVC filters for the treatment of DVT. **Indications for placement of IVC filters are as follows: a contraindication to anticoagulation,**

a complication from anticoagulation, or recurrent thromboembolization despite adequate anticoagulant therapy. Relative indications for IVC filters are massive PE, iliofemoral DVT, free floating proximal DVT, cardiac or pulmonary insufficiency, high risk of complications from anticoagulation (frequent falls and ataxia), or poor compliance. **Retrievable** filters can be considered for situations in which anticoagulation is temporarily contraindicated or there is a short duration of PE risk. **IVC filter alone is not an effective therapy** for DVT, and resumption of anticoagulation as soon as risk of bleed is acceptable is recommended.

- c. **Duration of treatment.** The **duration** of treatment following the diagnosis of DVT is **dependent on the risk of recurrence**. Risk factors for recurrence include an idiopathic DVT, underlying hypercoagulable states (listed in subsequent text), and malignancy. In addition, placement of a permanent IVC filter, elevated D-dimer levels, advanced age, male sex, and increased BMI also place individuals at a higher risk for recurrence. The risk of recurrence is low while patients are on anticoagulation; however, clinicians must weigh the risk of bleeding against the risk of new thrombosis.

Current guidelines **recommend 3 months of anticoagulation** with a VKA targeting an **INR of 2 to 3** for patients with a **first episode of DVT secondary to a transient cause**. Anticoagulation with a VKA for at least **6 to 12 months** with a target **INR of 2 to 3** is recommended for patients with a **first episode of idiopathic DVT**, although consideration should also be given for indefinite anticoagulation in this situation. Patients with the antiphospholipid syndrome, homozygous for FVL, or doubly heterozygous for FVL and prothrombin gene mutation should be considered for **indefinite anticoagulation**. Long-term (indefinite) anticoagulation is also recommended in patients with malignancy for as long as the cancer remains active, and in patients who have unexplained recurrent DVTs.

6. **Calf vein thrombosis.** Anticoagulation is generally indicated for symptomatic calf vein DVT or when there is propagation into the **popliteal vein or more proximally**. Current guidelines recommend 3 months of treatment with a VKA targeting an INR of 2 to 3 for patients with a first episode of symptomatic DVT confined to the calf veins secondary to a transient cause. Monitoring calf vein thrombosis for propagation into the proximal veins with serial ultrasonography (once or twice weekly for 2 to 3 weeks) without anticoagulation represents an alternative approach to treatment for individuals with high risk of bleeding.
7. **Superficial venous thrombosis** frequently occurs as a complication of an IV line in an upper extremity, but may occur spontaneously in the upper or lower extremities. Anticoagulation is generally not required due to the lower risk of PE, unless the thrombosis propagates into the deep venous system or if the event is spontaneous. Guidelines recommend intermediate doses of heparin or LMWH for at least 4 weeks for spontaneous superficial thrombophlebitis. Alternatively, a VKA can be used for 4 weeks. A recent study showed that daily fondaparinux at a dose of 2.5 mg for 45 days was effective in the treatment of lower extremity symptomatic superficial thrombophlebitis without serious side effects.
8. **Upper extremity DVT.** Upper extremity DVT is most often related to central venous catheter placement and/or pacemaker devices. Other less common causes include thoracic outlet syndrome, Paget-von Schrötter syndrome (also referred to as effort thrombosis), and hypercoagulable conditions including malignancy. Patients may be asymptomatic but more frequently complain of arm swelling and pain. Anticoagulation is indicated if there are no contraindications. Thrombolysis should be considered in younger patients with effort thrombosis, who have a low risk of bleeding and symptoms of acute onset. Determination of the length of anticoagulation with a VKA should be decided using the same processes described for acute lower extremity DVTs.

B. PE. It is difficult to approximate the true incidence of PE, but there are estimates that as many as 300,000 Americans have a fatal PE each year and as many as 34% of affected individuals present with sudden death. **The majority of patients die because of a failure in diagnosis rather than inadequate therapy.** In fact, the mortality rate for PE without treatment is approximately 30%, whereas it is only 2% to 8% with adequate treatment. PE remains the most common preventable cause of hospital death in the United States.

1. **Pathophysiology and symptoms.** Hemodynamic collapse related to PE results from a combination of vascular obstruction from thrombus and vasoconstriction caused by inflammatory mediators and hypoxia. Elevated pulmonary vascular resistance results in decreased right ventricular outflow, leading to a decrease in preload and cardiac output resulting in hypotension. To overcome an obstruction of 75% and maintain pulmonary perfusion, the right ventricle must generate a systolic pressure in excess of 50 mm Hg and a mean pulmonary artery pressure > 40 mm Hg. The normal right ventricle is unable to generate these pressures, and right heart failure and cardiac collapse ensue. In addition, elevated right ventricular wall tension can lead to decreased right coronary artery flow and ischemia. Cardiopulmonary collapse from PE is more common in patients with coexisting coronary artery disease (CAD) or underlying cardiopulmonary disease.

PE may present as one of the following three syndromes: (a) **acute cor pulmonale**, (b) **pulmonary infarction**, or (c) **dyspnea**. Patients presenting with acute cor pulmonale, as manifested by the sudden development of dyspnea, cyanosis, shock, or syncope, usually have a massive PE leading to cardiovascular collapse. Patients with pulmonary infarction usually present with pleuritic chest pain, dyspnea, and hemoptysis, and an audible friction rub may be heard. The majority of patients present with generalized symptoms of chest pain, dyspnea, and malaise.

2. Diagnosis

- a. Several pretest probability scores have also been developed for the diagnosis of PE similar to those for the diagnosis of DVT. In a validation study of the Wells clinical decision rule, only 0.5% of patients who were unlikely to have PE and had a negative D-dimer had subsequent nonfatal VTE.
- b. **Troponin.** Cardiac troponins have been evaluated in the setting of acute PE, and elevated levels correlate with electrocardiographic and echocardiographic findings of right ventricular pressure overload. Elevations in this marker can be seen in patients with and without CAD, but the overall mortality and in-hospital complications are higher in patients with acute PE and elevated cardiac troponin than in patients without elevated cardiac troponin.
- c. **Brain natriuretic peptide** elevation in the absence of renal dysfunction is also a marker of right ventricular dysfunction in patients with PE. Like elevated troponin levels, these elevated levels have also been shown to be predictors of adverse outcome in patients with acute PE.
- d. **Arterial blood gas.** PE can result in significant hypoxia, but in the Prospective Investigation of Pulmonary Embolism Diagnosis (PIOPED) study, 26% of patients with angiographically proven PE had $\text{PaO}_2 > 80$ mm Hg. Similarly, a **normal alveolar-arterial gradient does not preclude the diagnosis of PE.** Therefore, a normal PaO_2 cannot rule out PE; however, hypoxia in the absence of cardiopulmonary disease should raise the suspicion for this diagnosis. In patients with cardiopulmonary collapse, a normal PaO_2 suggests that PE is an unlikely cause.
- e. **Chest radiography** may be more helpful in establishing other diagnoses. When present, findings are nonspecific and include pleural effusion, atelectasis, and consolidation. The classic signs, including the Westermark sign (regional oligemia), Hampton's hump (pleural-based, wedge-shaped shadow), and Palla's sign (enlarged right inferior pulmonary artery), are uncommon.

- f. **Electrocardiography.** Like chest radiography, the major utility of the electrocardiogram (ECG) in the diagnosis of PE is to rule out other major diagnoses, such as acute myocardial infarction (MI). The most specific finding on an ECG is the classic $S_1Q_3T_3$ pattern, but the most common findings are non-specific ST-segment and T-wave changes. Other commonly reported findings include sinus tachycardia, atrial fibrillation, and right bundle branch block.
- g. **Echocardiography.** More than 50% of hemodynamically stable patients with PE will not have evidence of right ventricular dysfunction on transthoracic echocardiography (TTE). Patients with **hemodynamic collapse, however, will generally have severe right ventricle dysfunction**, and TTE can provide rapid bedside assessment in these critically ill patients. TTE findings include right ventricular dilation, right ventricular hypokinesis, tricuspid regurgitation, septal flattening, paradoxical septal motion, diastolic left ventricular impairment secondary to septal displacement, pulmonary artery hypertension, lack of inspiratory collapse of the IVC, and, rarely, direct visualization of the thrombus. In patients with large PE, it has been observed that despite moderate or severe right ventricular free wall hypokinesis there is relative sparing of the apex. This finding is referred to as **McConnell's sign** and has a specificity of 94% and a positive predictive value of 71% for PE. McConnell's sign may be useful in discriminating right ventricular dysfunction due to PE versus other causes.
- h. **Ventilation–perfusion (V/Q) scanning.** V/Q scanning is now considered a second-line imaging method for the diagnosis of PE. V/Q scans are helpful in patients who have normal chest radiography or who are unable to have CT scanning, such as those with renal insufficiency, contrast allergy, or pregnancy. The results of PIOPED suggest that V/Q scanning is helpful if the scan is normal or at high probability for PE (87% of patients with high-probability scans had PE, but only 4% of patients with normal scans had PE). Intermediate-probability or low-probability scans are the most common finding, however, occurring in approximately 70% of patients in the PIOPED study. In addition, patients who had a high or intermediate clinical suspicion for PE but a low-probability scan still had a 40% and 16% rate, respectively, of PE diagnosed by pulmonary angiography. Hence, it is currently advised that **patients with a high or intermediate clinical suspicion for PE but a low-probability V/Q scan have additional tests to confirm or refute the diagnosis**.
- i. **Computed tomography pulmonary angiography (CTPA).** Because of its wide availability and the ability to directly visualize thrombus, **CT imaging has become the standard imaging technique for the diagnosis of acute PE**. CTPA not only allows direct visualization of the thrombus but also has great value in excluding other diseases, including aortic dissection, pneumonia, or malignancy. It is especially useful in evaluating central PE (thrombus is seen as an intraluminal filling defect), and although the diagnostic yield for peripheral or subsegmental PE was low initially, the use of multidetector CTPA has greatly increased its sensitivity and specificity for the diagnosis of small peripheral or subsegmental PEs. CT venography of the abdomen and pelvis can also allow direct evaluation of the IVC and pelvic veins. This may be of value in selected cases as recent studies have shown that the routine use of CT venography of the pelvis during CTPA does not significantly improve the detection of VTE and therefore should not be performed routinely in all patients being evaluated for PE. The major disadvantages of CT are radiation exposure, higher cost, and the possibility of contrast-induced nephrotoxicity. A meta-analysis of 23 studies including 4,657 patients who were suspected of having PE but had normal CT scans found that only 1.4% developed VTE and 0.51% developed fatal PE by 3 months. These rates are similar to those in other studies involving patients who had suspected PE but were found to have normal pulmonary angiograms.

- j. **Pulmonary angiography** remains the gold standard diagnostic test for PE, but it is used infrequently due to the advent of CT scanning. Four injections with four views (right and left anteroposterior and right and left oblique) are performed. In some situations where a lung scan shows perfusion abnormalities and is nondiagnostic for PE, selective angiography of the abnormal area may be considered so as to limit the amount of contrast needed. In experienced centers, associated morbidity and mortality are low.
 - k. **Magnetic resonance angiography** (MRA) may be an alternative to CT for the diagnosis of PE in patients who have contrast allergy or for whom avoidance of radiation exposure is desired. In PIOPED III, MRA had insufficient sensitivity and a high rate of technically inadequate images. Addition of magnetic resonance venography (MRV) to MRA improves sensitivity; however, 52% of patients in the study had a technically inadequate study. At the current time, an MRA/MRV should be considered only at those centers with experience with this modality and only for patients for whom standard tests are contraindicated.
3. **Treatment.** Anticoagulation with heparin, LMWH, and fondaparinux followed by the addition of a VKA and supportive care has remained the standard of care in the management of acute PE. **Current guidelines recommend initial treatment with anticoagulants for patients with a high clinical suspicion for PE while awaiting the results of diagnostic testing.** For patients with nonmassive PE, subcutaneous LMWH, IV UFH, or fondaparinux are recommended as initial treatment. In patients with acute nonmassive PE, LMWH is recommended over UFH. A VKA may be initiated together with IV UFH, LMWH, or fondaparinux and should be continued for a minimum of 4 to 5 days and until the INR is stable and ≥ 2.0 .
- a. **Thrombolysis** for the treatment of acute PE is highly individualized, as there have been no clearly established short-term mortality effects. Because of favorable outcomes with prompt recognition and anticoagulation for PE, **thrombolysis should be reserved for hemodynamically unstable patients with acute massive PE and a low risk of bleeding.** It is unclear whether there is any benefit for thrombolytic therapy in patients who are hemodynamically stable but who have echocardiographic evidence of right ventricle dysfunction. Streptokinase, urokinase (no longer available in the United States), and tissue plasminogen activator are the current agents approved by the FDA. Current guidelines recommend the use of systemic thrombolytic therapy in patients who are hemodynamically unstable. Local administration of thrombolytic therapy via a catheter is not suggested, owing to the risk of hemorrhage at the insertion site.
 - b. Pulmonary embolectomy was the first definitive therapy to be performed for PE. There have been no randomized trials evaluating embolectomy, and the primary use of this procedure is in patients with shock and a contraindication to thrombolysis. Other investigational therapies include catheter-based embolectomy procedures that utilize aspiration, fragmentation, or rheolytic therapy. As of yet, there are currently no guidelines for the use of these therapies.
4. **New oral anticoagulants.** Until recently, warfarin was the only available oral anticoagulant for the treatment of VTE. Multiple new oral agents, with different mechanisms of action, have been evaluated in phase III clinical trials and have become available in markets outside the United States. These medications have the potential to revolutionize management of VTE. The agents that are most advanced in their development are the oral direct thrombin inhibitor (DTI), dabigatran etexilate, and oral direct factor Xa inhibitors (such as apixaban and rivaroxaban).

These new oral anticoagulants in general have a more rapid onset of action, which may obviate the need for parenteral anticoagulation in the initial treatment

of VTE. Additionally, because these agents have stable pharmacodynamics (unlike warfarin), routine monitoring is not required. This makes them more favorable for use as long-term anticoagulants. A major disadvantage of these medications, however, is the current lack of an antidote in case of bleeding complications.

- a. **Oral direct thrombin inhibitors.** Ximelagatran was the first oral DTI to complete phase III clinical trials; however, because of the high incidence of hepatotoxicity, it was withdrawn from the market.

Dabigatran etexilate—a prodrug—has been shown in a randomized, double-blind, noninferiority trial (RE-COVER) to be as effective as warfarin for the treatment of acute VTE with a similar safety profile. Dabigatran was given in a fixed dose without the need for laboratory monitoring. Dabigatran was also not inferior to subcutaneous enoxaparin in the prevention of VTE after total knee or total hip arthroplasty with similar bleeding risks. Dabigatran is not approved yet by the FDA for the prevention and treatment of VTE; however, it has been approved recently for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation based on the data from the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. It requires dose adjustments for patients with a creatinine clearance of 15 to 30 mL/min and is not recommended if the creatinine clearance is ≤ 15 mL/min.

- b. **Oral direct factor Xa inhibitors.** Rivaroxaban is an oral direct factor Xa inhibitor with a relatively short half-life of 5 to 9 hours and rapid onset of action of 2.5 to 4 hours.

Oral rivaroxaban given alone was not inferior to subcutaneous enoxaparin followed by warfarin for the treatment of acute symptomatic DVT, with a similar safety profile (EINSTEIN-DVT trial).

Rivaroxaban has also been shown to be superior to enoxaparin for the prevention of VTE following knee and hip replacement surgery, with a similar safety profile in the RECORD trials. It was recently approved by the FDA for the prevention of VTE in adults following hip and knee arthroplasty.

Rivaroxaban was also approved recently for the prevention of stroke and systemic embolization in patients with nonvalvular atrial fibrillation based on the results of ROCKET-AF trial. It should not be used in patients with severe renal insufficiency or significant hepatic impairment.

Apixaban is another oral direct factor Xa inhibitor with promising data. Apixaban was found to be comparable to warfarin in a small phase II trial for the treatment of DVT. Apixaban was superior to enoxaparin when given using the European regimen (40 mg daily starting on the evening before surgery) in preventing VTE after knee and hip replacement. However, in another study, apixaban failed to meet the noninferiority standards for the prevention of VTE after knee replacement when compared with enoxaparin (given in the North American regimen of 30 mg every 12 hours starting 12 to 24 hours after surgery). Abixaban has been approved in Europe for the prevention of VTE in adults following hip and knee arthroplasty but is not yet approved in the United States. Similar to dabigatran and rivaroxaban, abixaban will likely also be approved soon in the United States for the prevention of stroke in nonvalvular atrial fibrillation based on the data from ARISTOTLE trial.

- c. **VTE prophylaxis.** Thromboprophylaxis should be provided to all hospitalized patients. Unfortunately, studies show that less than half of hospitalized patients receive appropriate VTE prophylaxis. Individuals who are considered at greatest risk are those over 40 years and patients who are immobilized or who have an underlying medical conditions (MI, stroke, congestive heart failure, and pneumonia), suffered trauma, or have undergone recent surgical procedures (especially hip fracture, total knee or hip replacement, or neurosurgical procedures). There are two major forms of prophylaxis, **mechanical and pharmacologic**. Those who cannot receive prophylactic anticoagulation should be prescribed mechanical modalities such as intermittent pneumatic

compression devices. Pharmacologic prophylaxis can be achieved by a number of agents, including UFH, LMWH, fondaparinux, a VKA, and rivaroxaban, which has been approved recently for VTE prophylaxis after hip and knee replacement surgery. Other new oral anticoagulant agents (dabigatran and apixaban) are available outside the United States for prophylaxis and will likely be available sometime in the near future in the United States. In high-risk populations such as those with hip or knee replacement, a combination of mechanical and pharmacologic therapies should be considered. In select surgical procedures, extended prophylaxis is recommended. For example, extended prophylaxis for up to 28 to 35 days is recommended for patients who have had a hip fracture or who undergo total hip replacement surgery.

II. HYPERCOAGULABLE CONDITIONS. Conditions that predispose persons to an increased risk of thrombosis are referred to as hypercoagulable states or thrombophilia. These conditions are being identified more frequently and may be classified as inherited or acquired. Hypercoagulability testing should be considered in individuals with idiopathic VTE, family history of clotting, a first thrombotic event before the age of 50 years, thrombosis at unusual locations, resistance to anticoagulation, and those with recurrent thromboses.

A. FVL and prothrombin gene mutation. Activated PC inactivates factors Va and VIIIa and is one of the mechanisms by which the balance between clotting and bleeding is maintained. The autosomal dominant acquisition of a single-point mutation (FVL) in the factor V gene renders the protein factor V resistant to inactivation by activated PC. Both homozygous and heterozygous states are at an increased risk of venous thrombosis, with a 50-fold to 100-fold increase in the homozygous state and a 3-fold to 7-fold increase in the heterozygous state. The FVL mutation is more prevalent in persons of European and Scandinavian ancestry.

The prothrombin gene mutation G20210A (PT G20210A) is also inherited as an autosomal dominant mutation and may lead to a higher plasma level of prothrombin. It is also more common in those of Caucasian ancestry and confers a 2.8-fold increased risk of VTE. The role of FVL and PT G20210A mutations in arterial thrombosis is unclear. There is only a modest association between inherited thrombophilias and major arterial thromboses such as MI, stroke, or peripheral arterial disease. Therefore, routine screening for these mutations is not warranted in most patients with arterial thrombosis. In young persons who develop arterial events, however, abnormalities in hemostasis may play a role, particularly in the presence of other risk factors such as smoking and OCP use, and additional testing may be warranted. FVL and PT G20210A are associated with VTE during pregnancy, OCP use, and HRT. For example, the annual risk of DVT is 3 per 10,000 in women without FVL who use OCPs, 5.7 per 10,000 in women with FVL who do not use OCPs, and 28.5 per 10,000 in women with FVL who use OCPs. FVL can be identified by evaluating for activated PC resistance in plasma or by gene analysis using polymerase chain reaction. The prothrombin gene mutation is also identified by genetic analysis. There are no clear evidence-based guidelines for managing patients with thrombosis in the setting of these thrombophilias. In general, acute thrombosis should be managed in a standard fashion, but the duration of therapy is less clear, and the benefits of long-term anticoagulation must be weighed against the risks of bleeding. Current guidelines recommend **long-term therapy for patients who are homozygous for FVL or who are doubly heterozygous for FVL and PT G20210A**, as well as individuals with the **antiphospholipid syndrome**. Asymptomatic gene carriers should receive prophylaxis in high-risk situations.

B. Defects in the natural anticoagulants (PC, PS, and AT). Deficiency of any of the three natural anticoagulants is associated with an increased risk of venous thrombosis. All are inherited as autosomal dominant defects and are further subclassified based on reduction in their levels or defective quality of the protein. PS acts as a cofactor in the inactivation of factors Va and VIIIa by activated PC. It is bound to C4-binding protein (an acute phase reactant) in the plasma. Levels of PS and PC are lower in conditions such as disseminated intravascular coagulation (DIC), inflammatory states,

nephrotic syndrome, acute thrombosis, and liver disease. Pregnancy and OCP use can also decrease the levels of PS. Both PC and PS levels are lowered by warfarin therapy, and, therefore, these tests should not be assayed in patients who are receiving VKAs. Similarly, initiation of warfarin therapy without concomitant anticoagulation in the setting of acute VTE may lead to warfarin-induced skin necrosis (manifested as painful necrosis of the skin, primarily in fatty areas including the breast, buttocks, and thighs). Treatment includes stopping warfarin, administering vitamin K and fresh frozen plasma to replete levels, and using an alternative anticoagulant. AT is produced by the liver and endothelial cells and functions by inactivating thrombin and factors Xa, IXa, XIa, and XIIa. Homozygous states are incompatible with life. Levels are also low in the following: those with DIC, sepsis, liver disease, nephrotic syndrome; with the use of OCPs; and during pregnancy. As previously discussed, patients with AT deficiency may have resistance to heparin because it exerts its anticoagulant effect through AT. AT concentrates are available and can be used temporarily to correct this deficiency.

- C. Homocysteine.** Hyperhomocysteinemia is a risk factor for venous and arterial thromboses. It may be inherited, and genetic defects causing a deficiency of cystathionine β -synthase or a mutation in methylenetetrahydrofolate reductase have been reported. Acquired causes include deficiencies in vitamin B₁₂, B₆, or folate; smoking; and liver or renal failure. Treatment with folate in doses between 0.5 and 5 mg is usually effective in reducing the levels of homocysteine; however, this does not reduce the risk of major cardiovascular events, symptomatic venous thrombosis, or recurrent venous thrombosis.
- D. Heparin-induced thrombocytopenia.** HIT is a common, underrecognized but potentially devastating condition in patients who receive heparin or LMWH. The reported incidence is between 3% and 5% in patients exposed to UFH and lower (< 1%) in patients exposed to LMWH. The pathogenesis of HIT involves the formation of antibodies (usually immunoglobulin G [IgG]) against a heparin-platelet factor 4 (PF4) complex. The HIT antibodies then trigger procoagulant effects through platelet and endothelial cell activation, as well as thrombin generation leading to both microvascular and macrovascular thromboses. The clinical spectrum of HIT ranges from isolated thrombocytopenia without thrombosis (referred to as isolated HIT) to HIT(T), which is associated with both arterial and venous thromboses. Other manifestations of HIT may include hypotension from adrenal hemorrhage secondary to adrenal vein thrombosis and ensuing infarction, skin necrosis at injection sites, or venous limb gangrene. HIT should be suspected in any patient who develops thrombocytopenia while receiving heparin or LMWH; any patient who develops a < 50% decline in platelet count after the initiation of either anticoagulant; or any patient who develops new thrombosis or extension of an existing thrombosis while receiving either of these agents. In patients with HIT and de novo exposure to heparin, thrombocytopenia (platelet count < 150,000 per μ L) usually occurs between days 5 and 14 (with day of heparin exposure being day 0). In patients with a recent exposure to either agent (generally within the last 100 days), HIT may develop sooner and is referred to as rapid-onset HIT. This complication may also develop 9 to 40 days after heparin or LMWH has been discontinued and is known as delayed-onset HIT. Laboratory tests to aid in the diagnosis of HIT include functional assays (detection of heparin-dependent platelet activation in the presence of UFH or LMWH), such as heparin-induced platelet aggregation and serotonin release assays (SRA), and antigen assays (immunoassays), which detect IgG, IgM, or IgA antibodies that bind UFH to PF4. The SRA has the highest sensitivity and specificity for the diagnosis of HIT. The first step in the treatment of HIT is the prompt discontinuation of all sources of heparin or LMWH, including heparin flushes, heparin-coated catheters, any intermittent use of heparin during dialysis, and total parenteral nutrition or angiography. However, approximately 20% to 53% of patients with HIT will develop thrombosis (many within the first month) when treated only with discontinuation of heparin or LMWH alone. Therefore, the

initiation of an alternative anticoagulant, unless contraindicated, is recommended. **DTIs**, including lepirudin and argatroban (both approved by the FDA), may be used initially. Lepirudin has a longer half-life and is metabolized primarily by the kidney. The aPTT can be used to monitor therapy with a target range of 1.5 to 2.5 times the baseline level measured 4 to 6 hours after dose adjustments. Argatroban has a shorter half-life than lepirudin and is primarily metabolized in the liver. The goal for aPTT is 1.5 to 3.0 times the baseline level. There are no agents available that reverse the effects of either drug; therefore, if bleeding develops, prompt discontinuation should be considered. Once platelet counts are more than 100,000 to 150,000 mm³, warfarin may be started at a low dose (2.5 to 5 mg preferred). Early introduction or higher doses of warfarin may lead to venous limb gangrene or warfarin-induced skin necrosis. Overlapping the DTI with the VKA should be continued for at least 5 days and not discontinued until the INR is therapeutic for two consecutive days. Argatroban falsely elevates the INR; therefore, it should not be discontinued until INR > 4, as recommended by the manufacturer. After cessation of argatroban, the INR should be rechecked within a few hours to confirm that it is between 2 and 3. The duration of anticoagulation for patients with HIT is generally determined by the location and type of thrombosis. In patients without thrombosis (isolated HIT), the duration of anticoagulation is less clear, but given the high incidence of thrombosis within the first month, it is reasonable to continue anticoagulation for at least a month in the absence of contraindications.

- E. Antiphospholipid antibodies** are a heterogeneous group of autoantibodies that, if present in a patient with thrombosis, lead to the antiphospholipid syndrome. Antiphospholipid antibodies can be divided into three groups: (a) anticardiolipin antibodies, (b) lupus anticoagulants, and (c) β_2 glycoproteins. They are often associated with other autoimmune conditions and can cause recurrent pregnancy loss, as well as arterial or venous thrombosis. Thrombocytopenia is also an occasional feature of this syndrome. Anticardiolipin antibodies are detected and quantified using an enzyme-linked immunosorbent assay and may be IgG, IgM, or IgA. IgG titers have been correlated more often with thrombosis. Lupus anticoagulants prolong phospholipid-dependent blood clotting times, and it has been reported that there is about a fivefold increased risk of thrombosis in patients with this finding. Once a thrombotic event occurs, long-term therapy with warfarin must be considered. A higher target INR had been considered necessary in the past (approximately ≥ 3.0), but is no longer considered necessary as data have suggested that most patients can be maintained with a target INR of 2.0 to 3.0. In those individuals that are suspected of failing adequate therapy, one strategy is to correlate the INR to factor II and factor X levels (of $\leq 20\%$ to 30%) to ensure adequate anticoagulation. Patients with recurrent miscarriages should receive aspirin and LMWH during pregnancy.
- F. Malignancy.** Many malignancies induce a hypercoagulable state, and in patients with idiopathic VTE, a search for age- and gender-specific malignancies may be necessary. LMWH as monotherapy for the first 3 months before bridging to Coumadin has been shown to decrease the risk of venous thrombosis recurrence or anticoagulation failure.
- G. Other conditions.** Elevated factor VIII levels and the dysfibrinogenemias have also been associated with thrombosis; however, the role of deficiencies of plasminogen, tissue plasminogen activator (of the fibrinolytic system), and factor XIII polymorphisms as emerging risk factors for hypercoagulability is less clear.

ACKNOWLEDGMENTS: *The authors acknowledge the contributions of Dr. Vijay Nambi and Dr. John Bartholomew to earlier editions of this chapter.*

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CHAPTER

26

Matthew C. Bunte
Maran Thamilarasan

Aortic Aneurysm and Aortic Dissection

I. INTRODUCTION

- A. Aorta.** The aorta is the **principal conductance vessel** in the body and is divided into the ascending, arch, descending thoracic, and abdominal components.
1. The **ascending aorta** includes the aortic root, which contains the sinuses of Valsalva. The left and right coronary arteries arise from the left and right coronary sinuses, respectively.
 2. The **aortic arch** gives rise to the great vessels of the head and arms. These include the brachiocephalic (innominate), the left common carotid, and the left subclavian arteries.
 3. The **descending thoracic aorta** provides the intercostal vessels as it courses through the posterior mediastinum. The vascular supply to the anterior spinal artery is included among these vessels.
 4. The **abdominal aorta** begins just after the aorta crosses the diaphragm. It provides the splanchnic and renal arteries before bifurcating to become the common iliac arteries.
- B. Histology.** The aorta comprises **three layers**: the intima, the media, and the adventitia.
1. The **intima** is the internal lining layer of the aorta and is easily damaged.
 2. The **media** is the main structural layer of the aorta. It consists primarily of laminar layers of elastic tissue and smooth muscle in varying amounts. This structure allows for the high tensile strength and elasticity required to withstand the pressure changes of each heartbeat throughout the life of the individual.
 3. The **adventitia** is the thin outer layer that anchors the aorta within the body, in addition to providing nourishment to the outer half of the wall through the vasa vasorum.

C. Physiology

1. The **elasticity of the aortic wall allows it to distend** under the pressure created during ventricular systole. In this way, the kinetic energy that was developed during ventricular systole is stored as potential energy in the distended aortic wall. Then, during ventricular diastole, the potential energy is converted back to kinetic energy by elastic recoil of the wall. Therefore, forward blood flow is maintained throughout the cardiac cycle.
 2. The aorta aids in the control of **systemic vascular resistance (SVR)**. Pressure receptors in the ascending aorta and aortic arch signal the vasomotor centers of the brain via the vagus nerve. When blood pressure is elevated, the reflex response is to lower heart rate and decrease SVR. The converse is true when blood pressure is decreased.
- D. Acute aortic syndromes including aortic dissection, aortic intramural hematoma (IMH), and penetrating atherosclerotic ulcer (PAU) are life-threatening disorders that require prompt diagnosis and treatment.**
- E. The 2010 ACC/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM Guidelines for the Diagnosis and Management of Patients with Thoracic Aortic Disease is the principal source of information discussed in this chapter. Where appropriate and unless otherwise indicated, class I guideline recommendations from this document are embedded in italics within this chapter. The level of evidence following the corresponding recommendation is provided in parenthesis.**

II. AORTIC DISSECTION

- A. The International Registry of Acute Aortic Dissections (IRAD).** Since 1996, the IRAD has built a consortium of 24 referral centers in 12 countries dedicated to the study of acute aortic dissection that now includes over 1,600 patients. This research collaborative has provided considerable insight into and improvement in the management and outcomes of acute aortic dissection. More information about IRAD can be found at www.iradonline.org.
- B. Etiology and pathology**
1. **Aortic dissection classically occurs when a tear in the intima results in separation of the intima from the media (90% of cases), forming a false lumen within the aortic wall. Less commonly, rupture of the vasa vasorum within the aortic wall may result in separation of the intima and media, thereby causing dissection. In either case, acute aortic dissection results from a pathologic weakening of the aortic wall due to medial necrosis, atherosclerosis, or inflammation.** There are many risk factors for aortic dissection, although the most common is a history of systemic hypertension as evidenced in over 70% of cases. Younger patients suffering aortic dissection are more likely to have a genetic or morphologic risk factor, such as genetic syndromes associated with aortopathy, bicuspid aortic valve (BAV), or prior aortic surgery. The following list includes the most common conditions associated with aortic dissection:
 - a. Increased age and uncontrolled hypertension are the two most common risk factors.
 - b. Tobacco use, dyslipidemia, and cocaine use are important risk factors.
 - c. Genetic diseases, especially Marfan, Loeys-Dietz, and vascular-type Ehlers-Danlos syndromes, are associated with aortic aneurysm and dissection.
 - d. Familial thoracic aortic aneurysm (TAA) and dissection syndrome and other congenital anomalies associated with aortic aneurysm and dissection, including BAV and Turner syndrome.
 - e. Inflammatory vasculitides, including Takayasu arteritis, Giant cell arteritis, and Behçet arteritis.
 - f. Infections involving the periaortic tissue, as seen in prosthetic aortic valve endocarditis.

- g. Aortic trauma, particularly with deceleration and torsional injuries, although may occur with direct endoluminal trauma during arterial catheterization or with cardiothoracic surgery.
 - h. Pregnancy.
2. **Genetic syndromes associated with aortic aneurysm and dissection.** Marfan, Ehlers-Danlos, and Loeys-Dietz syndromes are associated with an increased risk of aortic dissection. **These patients require comprehensive aortic imaging at diagnosis and heightened surveillance to follow aortic diameter owing to the increased risk of complications related to aortic disease.** *Aortic imaging is recommended for first-degree relatives with TAA and/or dissection to identify those with asymptomatic disease (Level of Evidence: B).*
- a. **Marfan syndrome.** Marfan syndrome is a genetic disorder with high penetrance and variable expression affecting connective tissue. Marfan syndrome is associated with mutations of the *FBNI* gene, which encodes fibrillin-1, a large glycoprotein that contributes to the structure of the extracellular matrix and serves as a regulator of transforming growth factor-beta (TGF- β). The principal features of Marfan syndrome involve the cardiovascular, ocular, and skeletal systems, with patients at exceedingly high risk for aortic disease. In fact, nearly all patients with Marfan syndrome demonstrate some form of aortic disease during their lifetime.
 - b. **Loeys-Dietz syndrome.** An autosomal dominant disorder associated with a triad of arterial tortuosity and aneurysm, hypertelorism, and bifid uvula, Loeys-Dietz syndrome results from mutations in either TGF- β receptor type 1 or 2 (*TGFBR1* or *TGFBR2*). Vascular disease among these patients is highly prevalent, with 98% demonstrating aortic root aneurysms, and portends a grim prognosis. Early reports of Loeys-Dietz syndrome suggested a particularly aggressive disease process with arterial complications occurring at a mean age of 26 years. However, subsequent data have revealed less aggressive phenotypes with later presentations, and a mean age of death closer to the fifth decade among less severe phenotypes. Repair of the aortic root is recommended at lesser aorta diameters (< 5.0 cm) due to the aggressive nature of this condition.
 - c. **Ehlers-Danlos syndrome, type IV (vascular form).** The vascular form of Ehlers-Danlos syndrome is characterized by an autosomal dominant inheritance of the *COL3A1* gene mutation that encodes type III procollagen. Clinical features include easy bruising and rupture of the uterus, intestines, and arteries. Median survival is 48 years and often no aneurysms are documented. Gravid women with this condition have a particularly poor prognosis during childbirth due to the high risk of arterial and uterine rupture.
3. **Hereditary conditions and congenital anomalies** such as BAV and coarctation of the aorta are also established risk factors for aortic dissection. Turner syndrome is associated with BAV (10% to 25%), aortic coarctation (8%), and dilatation of the ascending aorta. Although patients with Turner syndrome require screening for aortic disease at diagnosis, requirements of surveillance for aortic dilatation follow those of other patients with BAV. *All patients with BAV should have both the aortic root and ascending aorta evaluated for evidence of aortic dilatation (Level of Evidence: B). First-degree relatives of patients with a BAV, premature onset of thoracic aortic disease with minimal risk factors, and/or a familial form of TAA or dissection should be evaluated for the presence of a BAV and asymptomatic thoracic aortic disease (Level of Evidence: C).*
4. **Vasculitides** associated with large vessel inflammation and aortitis contribute to medial degeneration of the aortic wall and may increase the risk of aortic dissection. Examples of these inflammatory disorders include giant cell arteritis, Takayasu arteritis, syphilis, and Behçet disease.

5. **Aortic dissection exhibits a strong association with pregnancy.** Among cases of aortic dissection in women < 40 years of age, up to half may present during the third trimester or early in the postpartum period. **Gravid women with Marfan syndrome and preexisting aortic root dilatation are at especially high risk for aortic dissection.**
 6. **Direct aortic trauma is associated with aortic dissection.** Blunt chest trauma, such as that occurring in a motor vehicle accident, may cause aortic transection or mural hematoma. Intravascular instrumentation as during arterial catheterization, insertion of an intraaortic balloon pump, or aortic cannulation, cross-clamping, and graft insertion may also serve as a source of intimal damage and dissection.
- C. Epidemiology.** The incidence of aortic dissection has been estimated from 2 to 3.5 cases per 10,000 person-years, corresponding to 6,000 to 10,000 cases per year in the United States. The male-to-female ratio approaches 3:1, with the peak incidence in the sixth and seventh decades of life. The mortality for untreated acute aortic dissection is largely determined by the location of the dissection, but overall mortality is approximately 1% per hour within the first 48 hours if surgery is not performed. Approximately 65% of dissections originate in the ascending aorta (just above the right or noncoronary sinus), 20% in the descending thoracic aorta, 10% in the aortic arch, and the remainder in the abdominal aorta.
- D. Classification schemes**
1. **Anatomic classification schemes** used to commonly describe aortic dissection include the DeBakey and Stanford systems (see Table 26.1 and Fig. 26.1 for a description of the DeBakey and Stanford classifications). Anatomic classification refers to the portion(s) of aorta involved. The Stanford classification will be used throughout this chapter.
 2. Dissections are further classified according to chronicity: acute (< 2 weeks from onset) or chronic (> 2 weeks from onset).
 3. Anatomic involvement and chronicity of dissection influence the recommended treatment approach and indicate prognosis.
 - a. **Type A dissection.** Predictors of death are age 70 years or older, abnormal electrocardiogram (ECG), pulse deficit, acute renal failure, and the composite of hypotension, shock, or tamponade.
 - b. **Type B dissection.** Predictors of death are branch vessel involvement, absence of chest or back pain, and hypotension/shock. Continued patency of the false lumen predicts a worse outcome in type B aortic dissection. The highest survival benefit is among those with complete thrombosis of the false lumen.

TABLE 26.1 Aortic Dissection Classification Systems

Classification	Pathologic description
Stanford	
Type A	Any dissection involving the ascending aorta
Type B	Any dissections <i>not</i> involving the ascending aorta
DeBakey	
Type I	Entry point in the ascending aorta, extends to the aortic arch and often beyond
Type II	Confined entirely to the ascending aorta
Type III	Entry in the descending aorta (distal to left subclavian); extends distally (usually) or proximally (rarely)

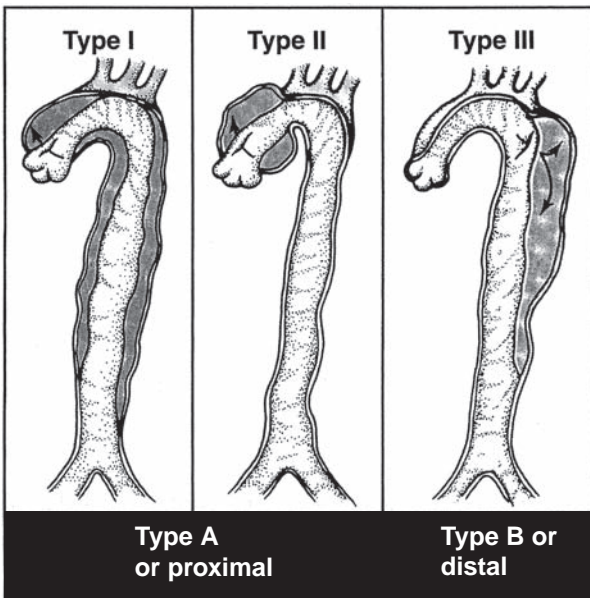


FIGURE 26.1 Anatomic appearance of three different aortic dissection classifications.

E. Atypical variants of aortic dissection

1. **IMH** represents a focal hemorrhage of the aortic wall caused by rupture of the vasa vasorum within the aortic wall and may cause secondary dissection. The natural history of IMH is similar to that of classic aortic dissection. In fact, in 4% to 10% of dissections, an intimal tear is not found. Therefore, *it is reasonable to treat IMH similar to de facto aortic dissection including surgery if located in the ascending aorta or aggressive medical therapy if in the descending aorta (Level of Evidence: C)*.
2. **PAU** is a focal defect in the endoluminal surface of the aortic wall produced by atherosclerotic erosion through the intima with ulceration into the media. Risk factors for PAU include older age, extensive atherosclerosis, and uncontrolled hypertension. PAU may manifest as subtle asymptomatic erosions noted incidentally on radiography to symptomatic IMH with eccentric or saccular aneurysms of the aorta. In either case, PAU may progress to aortic dissection or aortic perforation, although the natural history of this condition remains uncertain. Nevertheless, surgery is often recommended for patients exhibiting unstable symptoms or lesions involving the ascending aorta. Otherwise, medical management and frequent radiologic follow-up for signs of progression is recommended.

F. Clinical presentation

1. Signs and symptoms

- a. Aortic dissection may present with a wide range of clinical manifestations. Proximal dissections are most commonly characterized by a sudden onset of chest pain (80%) that is severe in intensity and ripping, tearing, stabbing, or sharp in quality. Pain may radiate to the interscapular region of the back (47%) or abdomen (21%). Among descending aortic dissections, back pain (64%), chest pain (63%), and abdominal pain (43%) are most common. **Typical symptoms are less common in the elderly.**

- b. Presenting clinical findings may include the murmur of severe aortic insufficiency (AI) (45%) associated with proximal aortic dissection and contributing to acute heart failure (5% to 6%), hypotension (14%) or shock (13%) associated with cardiac tamponade (5% to 10%), syncope (13%), myocardial infarction (MI) (7% to 19%) with retrograde dissection into the ostia of the coronary arteries, cardiovascular accident (CVA) (8%) with cephalad carotid extension, paraplegia (2%) with extension into the intercostal and spinal arteries, or cardiac arrest. Dissections involving the arterial supply to the limbs may contribute to pulse deficits (26%), acute limb ischemia (10%) with distal extension, and neuropathy.

G. Diagnostic testing

1. **Evaluation.** Figure 26.2 provides an algorithm to aid in diagnosis. Key characteristics important in defining the extent of aortic dissection and clinical management include ascending versus descending aortic involvement, site of the intimal tear, presence or absence of AI, presence of pericardial effusion and/or tamponade, coronary involvement, and involvement of visceral arterial supply. Computed tomography (CT), magnetic resonance imaging (MRI), transesophageal echocardiography (TEE), and invasive aortography are common imaging modalities useful in the diagnosis of acute aortic dissection. The relative advantages and disadvantages of the four modalities are outlined in Table 26.2. **Selection of the specific imaging modality for identification or exclusion of aortic dissection should be based on clinical variables, local expertise, and clinical availability to facilitate rapid diagnosis (Level of Evidence: C).**
2. *An ECG should be performed in all patients with suspected aortic dissection (Level of Evidence: B).* Most frequently, ECG is useful to exclude an acute coronary syndrome presenting atypically as symptoms of aortic dissection. *Because dissection-related acute MI is infrequent, ST-segment elevation on ECG should be treated as an independent coronary event without delay for aortic imaging unless the patient is at high risk for aortic dissection (Level of Evidence: B).*

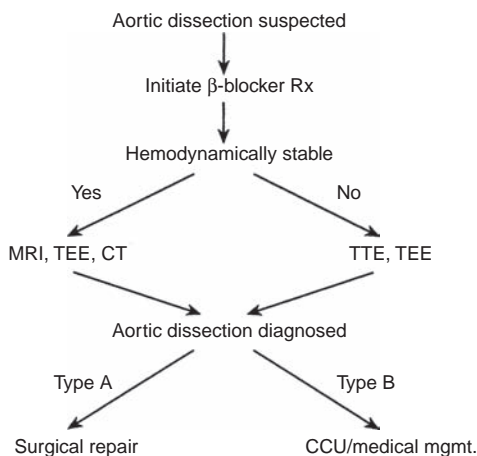


FIGURE 26.2 Aortic dissection diagnostic/therapeutic algorithm. CCU, coronary care unit; CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

TABLE 26.2 Comparison of Imaging Modalities in Aortic Dissection

Factor	Angiography	CT	MRI	TEE
Intimal tear definition	++	+++	+++	++
False lumen thrombus +/-	+++	+++	+++	+
Involvement of branch vessels	+++	++	++	+
Pericardial effusion	—	+++	+++	+++
Coronary involvement	+++	—	—	++
AI presence	+++	—	+	+++
Overall sensitivity (%)	88	100	98	98
Overall specificity (%)	95	98	98	95

AI, aortic insufficiency; CT, computed tomography; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography.

Modified from Isselbacher EM, Eagle RA, DeSanctis RW. Diseases of the aorta. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 5th ed. Philadelphia, PA: WB Saunders, 1997:1546–1581.

3. Chest radiography may occasionally detect findings suggestive of dissection, although it is inadequately sensitive to definitively exclude the presence of acute aortic dissection. *A negative chest x-ray should not delay definitive aortic imaging in patients determined to be high risk for aortic dissection by initial screening (class III recommendation, Level of Evidence: C).*

H. Selected imaging modalities for diagnosis of acute aortic dissection

1. **Computed tomography.** Contrast-enhanced, cardiac-gated multidetector CT is a widely available and the most commonly used imaging modality for the detection of aortic dissection, with excellent sensitivity and specificity approaching 100%. This modality has many advantages, including rapid scan and interpretation times. Disadvantages include iodinated contrast and radiation exposure.
2. **MRI and magnetic resonance angiography (MRA).** Like CT, MRI provides multiplanar imaging of the thoracic aorta with high sensitivity and specificity that is very accurate for diagnosis of acute aortic disease. MRA offers unique gadolinium-enhanced and black blood imaging techniques to evaluate aortic anatomy and morphology that prove particularly useful in assessing the aortic wall. Advantages of MRI include the ability to identify anatomic variants, such as IMH or penetrating aortic ulcer, assess branch arterial involvement, and provide useful information on aortic valvular and left ventricular systolic function while avoiding exposure to iodinated contrast or radiation. MRI is well suited for chronic follow-up of aortic syndromes since ionizing radiation is not necessary. Use of MRI is limited by availability, prolonged acquisition time, and incompatibility with implanted ferromagnetic devices. MRI is not an appropriate test for patients that are hemodynamically unstable.
3. **Transthoracic echocardiography (TTE) and TEE.** TTE allows for a rapid noninvasive evaluation, primarily of the proximal aorta with overall limited sensitivity and specificity. Visualization of the proximal aorta and other critical structures using TTE may be limited by factors that reduce image quality, such as emphysema, mechanical ventilation, and obesity. With an esophageal approach, TEE overcomes many of the challenges with improved sensitivity and specificity while offering a safe and rapid assessment of acute aortic disease. A major limitation of either TTE or TEE includes the appearance of ultrasound artifacts that may mimic a dissection flap, such as that of reverberation artifact.

4. **Invasive aortography.** Aortography offers accurate information about the location of dissection, providing visualization of the false lumen or intimal flap, branch vessel involvement, and communication between true and false lumens. Invasive aortography is useful in evaluating PAU, as it is characterized by endovascular aortic contrast protruding into an atherosclerotic plaque. False negatives can occur with thrombosis of the false lumen, IMH, or equal filling of the false lumen. Disadvantages of aortography include a low sensitivity, risks associated with any invasive procedure, contrast administration, and availability of experienced operators to perform the study.
5. **Recommendations for aortic imaging techniques to determine the presence and progression of thoracic aortic disease**
 - a. *Measurements of aortic diameter should be taken at reproducible anatomic landmarks, perpendicular to the axis of blood flow, and reported in a clear and consistent format (Level of Evidence: C).*
 - b. *For measurements taken by CT imaging or MRI, the external diameter should be measured perpendicular to the axis of blood flow. For aortic root measurements, the widest diameter, typically at the mid-sinus level, should be used (Level of Evidence: C).*
 - c. *For measurements taken by echocardiography, the internal diameter should be measured perpendicular to the axis of blood flow. For aortic root measurements, the widest diameter, typically at the mid-sinus level, should be used (Level of Evidence: C).*
 - d. *Abnormalities of aortic morphology should be recognized and reported separately even when aortic diameters are within normal limits (Level of Evidence: C).*
 - e. *The finding of aortic dissection, aneurysm, traumatic injury and/or aortic rupture should be immediately communicated to the referring physician (Level of Evidence: C).*
 - f. *Techniques to minimize episodic and cumulative radiation exposure should be utilized whenever possible (Level of Evidence: B).*
- I. **Therapy.** Death in aortic dissection results from vascular compromise, tamponade, or aortic rupture. **Management of proximal (type A) thoracic aortic dissection requires immediate surgical treatment to resect the entire aneurysmal aortic segment and the proximal extent of dissection (Level of Evidence: C).** Surgery greatly improves outcomes and avoids the risks associated with progression of dissection. One- and three-year survival after surgery for type A dissection is excellent, with survival rates of 96.1% and 90.5%, respectively. Survival rates at 1 and 3 years are 88.6% and 68.7%, respectively, among those who do not receive surgery for type A dissection. **Patients with distal (type B) thoracic and abdominal aortic dissections should be managed medically unless life-threatening complications, such as malperfusion syndromes, progression of dissection, aortic enlargement, or refractory hypertension, develop (Level of Evidence: B).** Percutaneous endovascular aortic repair (EVAR) is a technically feasible and potentially effective option for nonsurgical treatment of type B aortic dissection, although it has not been approved by the Food and Drug Administration (FDA) for this indication. Table 26.3 recommends the course of treatment for various types of dissections. The 5-year survival rate for patients leaving the hospital with appropriate treatment (medical or surgical) for type B dissection ranges from 75% to 82%.
 1. **Priority of therapy.** The initial management of patients with suspected aortic dissection is directed at **reducing aortic wall stress. Aortic wall stress is affected by the velocity of ventricular contraction (dp/dt), the rate of ventricular contraction, and blood pressure. Medical stabilization of acute aortic dissection should target the reduction of heart rate followed by lowering of blood pressure.** Invasive hemodynamic monitoring and sufficient intravenous access for volume replacement should be established simultaneously. An

TABLE 26.3 Surgical versus Medical Therapy for Aortic Dissection

Medical therapy	Surgical therapy	Endovascular therapy
Uncomplicated type B dissection	Acute, type A dissection	Malperfusion syndrome associated with type B dissection
Stable, lone arch dissection	Acute, complicated type B dissection	Possibly as an alternative to surgical therapy for complicated type B dissection
Stable, chronic type B dissection (> 2 wk after onset of symptoms)	End-organ dysfunction Rupture/impending rupture Aortic insufficiency Associated with Marfan syndrome Retrograde extension into the ascending aorta	Possibly as an alternative to medical treatment for uncomplicated type B dissection

initial and aggressive treatment approach to reduce dP/dt applies to all patients regardless of the location of dissection or whether the eventual management strategy is medical or surgical.

2. Medical therapy (see Table 26.4)

- a.** *With suspicion of acute aortic dissection, β -blockers should be initiated immediately and titrated to target heart rate of < 60 beats per minute*

TABLE 26.4 Intravenous Dosing for Acute Medical Management of Acute Aortic Syndromes

Drugs	Loading dose	Maintenance dose
First-line agents		
Propranolol	1 mg IV q3-5min (max. 6.15 mg/kg)	2–6 mg IV q4-6h
Labetalol	10 mg IV over 2 min, then 20–80 mg q10-15min (max 300 mg)	2 mg/min IV drip titrate to 5–20 mg/min
Esmolol	500 μ g/kg IV bolus	50–200 μ g/kg/min IV continuous
Metoprolol	5 mg IV q5min to effect	5–10 mg IV q4-6h to effect
Second-line agents in patients with contraindications for β-blockers		
Enalaprilat	0.625 mg IV	0.625 mg IV q4-6h
Diltiazem	0.25 mg/kg IV over 2 min; 0.35 mg/kg IV after 15 min if no effect	5 mg/h titrate by 2.5 to 5 mg/h increments; max 15 mg/h
Verapamil	0.075–0.1 mg/kg to 2.5–5 mg/kg over 2 min	5 to 15 mg/h IV drip

IV, intravenous.

(Level of Evidence: C). In patients who are intolerant of β -blockers, nondihydropyridine calcium channel blockers may serve as an acceptable alternative to control heart rate (see Table 26.4) (Level of Evidence: C). In the setting of acute aortic regurgitation, use of rate-controlling agents, such as β -blockers, should be used with caution since they block compensatory tachycardia (Level of Evidence: C).

- b. Once the heart rate goal has been achieved, systolic blood pressure should be targeted to < 120 mm Hg with the use of angiotensin-converting enzyme inhibitors or vasodilators to reduce blood pressure while maintaining adequate end-organ perfusion (Level of Evidence: C). With a goal of heart rate and blood pressure control, β -blockers with α -effect, such as labetalol, may be particularly advantageous. Sodium nitroprusside is a particularly useful vasodilator, given a rapid onset and easy titration as an intravenous infusion. Close monitoring for reflex tachycardia should be done with use of vasodilators—*vasodilator therapy should not be initiated prior to heart rate control since reflex tachycardia may increase aortic wall stress and risk of propagation or expansion of dissection (class III, Level of Evidence: C).*
3. **Managing complications of acute aortic dissection**
 - a. **Hypotension and shock.** Aortic wall rupture or hemorrhage into the pericardial space with cardiac tamponade may manifest as shock. In either event, **aggressive volume replacement should be initiated and the patient taken to the operating room promptly.** Pericardiocentesis is generally not recommended. If pericardiocentesis becomes an absolute requirement to get the patient to the operating room, enough pericardial fluid should be removed to raise the blood pressure to an acceptable level, but no more. **If vasopressors are required for hemodynamic stabilization, norepinephrine and phenylephrine are the drugs of choice, as neither has a demonstrable effect on dP/dt. Epinephrine and dopamine should be avoided.**
 - b. **Acute MI.** Coronary thromboembolism and retrograde progression of the aortic dissection flap into the coronary ostia are infrequent complications of proximal aortic dissection. In this setting, **thrombolysis is contraindicated.** Coronary arteriography and percutaneous intervention are not generally recommended since these procedures will **delay surgical repair of the dissection while exposing it to mechanical complications related to angiography in an already compromised aorta.**
 - c. **Refractory hypertension.** Sufficient blood pressure reduction can be difficult to obtain, with many patients requiring several antihypertensive drugs of different classes. Adequate analgesia is essential to reduce pain-related increases in sympathetic tone and blood pressure associated with acute aortic dissection. Following initial stabilization, use of β -blockers should be continued with consideration for angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists that may slow pathologic aortic dilatation.
 4. **Surgical management of acute aortic dissection**
 - a. *Patients with a proximal (type A) thoracic aortic dissection should receive emergent surgery. A partially dissected aortic root with a normal aortic valve may be repaired with supra commissural aortic valve resuspension. In the event that the aortic valve cannot be repaired or resuspended, a Bentall procedure may be performed with a prosthetic valve sewn onto a Dacron graft and used to replace the native valve with reimplantation of the coronary arteries into the graft (Level of Evidence: C).*
 - b. *Patients with type B dissection who have evidence of rupture or end-organ involvement should receive surgical repair with replacement of the entire segment of dissected aorta (Level of Evidence: C).* Reattachment of the visceral arteries and T_8 to L_2 intercostal/lumbar arteries are implanted into the graft conduit.
 - c. **Perioperative risk.** Compared with unstable patients with aortic dissection, those demonstrating preoperative stability have an improved prognosis.

Nevertheless, stable patients still carry a substantial surgical mortality of 17%. When patients have features of instability—such as cardiac tamponade, shock, congestive heart failure (CHF), cerebrovascular accident, coma, MI, acute renal failure, or mesenteric ischemia—surgical mortality rates rise to approximately 31%. Surgical mortality increases with age. However, the relative benefits of surgery outweigh risks of nonoperated type A dissection until at least the age of 80 years. Therefore, the benefits of surgery should be measured against surgical risks of all age groups, with consideration for complexity of repair, preoperative medical comorbidities, and anticipated quality of life after surgery.

d. **Postsurgical complications of open thoracic surgical repair** include respiratory failure (5% to 15%), stroke (2% to 8%), bleeding requiring reoperation (1% to 6%), infection (1% to 5%), MI (1% to 5%), heart failure (1% to 5%), ventricular arrhythmias (1% to 5%), acute postoperative renal failure, paraplegia (2% to 10%), and mesenteric ischemia.

(1) *A brain-protective strategy to prevent stroke and preserve cognitive function should be a key element of the surgical, anesthetic, and perfusion techniques used to accomplish repairs of the ascending aorta and aortic arch (Level of Evidence: B).*

(2) Paraplegia stands among the most feared complications of descending thoracic and thoracoabdominal aortic repairs, occurring in 2% to 4% and 3% to 10% of cases, respectively. Paraplegia results from the disruption of blood flow to the anterior spinal artery via the intercostal arteries. *Cerebrospinal fluid drainage is recommended as a spinal-protective strategy in open and endovascular thoracic aortic repair for patients at high risk for spinal cord ischemic injury (Level of Evidence: B).*

5. **Percutaneous EVAR for type B aortic dissection.** EVAR represents a technically feasible and potentially effective option for nonsurgical treatment of type B aortic dissection, although it has not received FDA approval for this indication and such use is considered “off-label.” Nevertheless, stent-grafting for conditions other than abdominal aortic aneurysm (AAA) is an area of active study, with proposed uses for EVAR in stable type B aortic dissection, IMH, PAU, acute traumatic aortic transection, and pseudoaneurysm.

a. **Potential advantages of EVAR** over conventional surgery include the absence of thoracotomy, avoiding cardiopulmonary bypass and clamping of the aorta, lower hospital morbidity rates, and shorter length of hospital stays. A mortality advantage of endovascular therapy was suggested in early trial reports, although it has largely been lost with longer-term follow-up from these studies.

b. **Comparing EVAR with optimal medical management (OMM).** Although OMM remains the mainstay for acute treatment of uncomplicated type B dissection, long-term morbidity and mortality of chronic dissection remain substantial. Data on EVAR for use in descending aortic dissection are limited. Results from a meta-analysis of 609 cases suggest that mortality rates are higher with EVAR (5.3%) compared with open surgical correction (2.5%), although the risk of major complications with either treatment is similar. Two prospective randomized trials have compared endovascular repair with OMM.

(1) The prospective INvestigation of STEnt grafts in patients with type B Aortic Dissection (INSTEAD) trial provided the first randomized evaluation of elective stent-graft placement in 140 patients with subacute or chronic uncomplicated type B aortic dissection. INSTEAD did not show a 2-year survival advantage or difference in adverse event rates with EVAR compared with optimal medical therapy.

(2) The optimal timing of EVAR for aortic dissection remains to be defined. The Acute Dissection Stent-grafting OR Best Medical Treatment

(ADSORB) trial is an ongoing study poised to compare EVAR with OMM for *acute* uncomplicated type B aortic dissection. Target enrollment is 250 patients with 3-year follow-up. Study completion is anticipated in 2015.

6. Postoperative surveillance after thoracic aortic repair or monitoring of chronic descending aortic dissection

- a. *CT or MRI of the thoracic aorta is reasonable after type A or type B aortic dissection or after prophylactic repair of the aortic root/ascending aorta (class IIa, Level of Evidence: C).*
- b. *CT or MRI of the aorta is reasonable at 1, 3, 6, and 12 months after dissection, then annually thereafter if clinically stable (class IIa, Level of Evidence: C).* In about 30% of cases, late deaths are caused by rupture of a secondary aneurysm or recurrence of the dissection. A majority of these secondary aneurysms will develop within 2 years of the initial treatment.
- c. *For patients with chronic dissection, particularly if associated with a connective tissue disorder, but without significant comorbid disease, and a descending thoracic aortic diameter exceeding 5.5 cm, open repair is recommended (Level of Evidence: B).*
- d. *Long-term, aggressive cardiovascular risk factor management is critical before and after thoracic aortic surgery and includes aggressive heart rate and blood pressure control to reduce dP/dt , lipid profile optimization, and smoking cessation (Level of Evidence: C).* In the event of medical treatment failure, including end-organ damage related to complications of aortic disease, aortic leak, or escalating visceral pain, patients with chronic descending aortic dissection should be considered for surgical treatment.

III. AORTIC ANEURYSM. An aortic aneurysm is a pathologic dilatation of the aorta to > 1.5 times its normal diameter. Aneurysms are classified based on involvement of the anatomic aortic segment, including AAA and TAA. The etiology, natural history, and treatments differ somewhat for aneurysms of each location.

A. Abdominal aortic aneurysm. Aneurysms of the aorta located below the diaphragmatic crura and above the bifurcation of the common iliac arteries are classified as AAA.

1. Etiology and pathology of aortic aneurysm

- a. **Aneurysms of the aorta are caused by degenerative disease within the aortic wall, leading to inflammation, weakening of the aortic tissues, loss of elasticity, and dilatation of the aorta.** Atherosclerosis has traditionally been linked with development of AAA, although the pathogenesis is likely multifactorial, involving immunologic, genetic, environmental, and hemodynamic factors. Matrix metalloproteinases and other proteases produced locally by smooth muscle cells may degrade elastin and collagen and lead to aneurysm formation.
- b. **Genealogic studies demonstrate a strong familial component to developing AAA,** with up to 28% of patients having a first-degree relative with an abdominal aneurysm. First-degree male relatives of patients with AAA have a 12 times greater risk of having an aneurysm.
- c. **Risk factors for the development of AAA** include current or past history of tobacco use, male gender, advanced age, first-degree relative with AAA, hypertension, hyperlipidemia, and atherosclerosis in other vascular beds. Less common causes include infection (*Salmonella* and *Staphylococcus aureus*), vasculitis, and trauma.
- d. **Rate of enlargement is dependent on aneurysmal diameter.**

- (1) Rate of enlargement can range from 0.2 cm/y to > 3 cm/y. The majority of aneurysms enlarge at a rate of 2.6 mm/y. **The larger the aneurysm grows, the faster it will continue to expand.**

- (2) Laplace's law defines the parameters for growth of aneurysms.

$$\text{Wall tension} = \text{transmural pressure (TP)} \times \text{radius (r)}$$

- (1) Therefore, with luminal dilatation (increased r), the wall tension will increase at a given blood pressure (TP). This leads to a further increase in radius and to a self-perpetuating cycle of growth of the aneurysm.

e. **Characteristics of aneurysmal rupture:**

- (1) *Risk is proportional to aneurysm size. Aneurysms > 6.0 cm have > 20% per year risk of rupture, whereas those between 5 and 6 cm have approximately 6% risk of rupture per year.*
- (2) Rupture usually occurs into the left retroperitoneal space (80%). Rupture in this location may initially be contained, although it will ultimately extend, causing shock and death if untreated.
- (3) AAA can also rupture into the inferior vena cava (causing aortovenous fistula formation). Fistulous connection between an enlarging aortic aneurysm and the gastrointestinal tract may create an aortoenteric fistula that may present as a life-threatening emergency requiring prompt surgical intervention. **A gastrointestinal bleed with known AAA or history of AAA repair should prompt consideration for an aortoenteric fistula.**
- (4) **Rupture of an AAA is associated with high mortality.** One-quarter of patients with rupture die before reaching the hospital and 50% die prior to undergoing surgery. Among those who survive to undergo surgery, the operative mortality approaches 50%.

2. **Epidemiology**

- a. **AAA is much more common than TAA, as nearly 75% of aneurysms involve the abdominal aorta.**
- b. **AAA affects men more commonly than women.** Among patients over age 65 years, the prevalence of AAA among men and women is 5% and 1.0% to 2.2%, respectively. The incidence of AAA increases after age 55 years in men and 70 years in women. Most cases (95%) involve the infrarenal aorta.

3. **Clinical presentation.** The majority of AAAs are discovered incidentally on physical examination or during radiologic evaluation of the abdomen.

- a. **Signs and symptoms.** Most patients are asymptomatic; therefore, the diagnosis of AAA should be considered in patients with an appropriate risk profile and family history.

- (1) Rapid enlargement of the aneurysm may be associated with severe back or flank pain and herald impending rupture. Pain associated with an expanding AAA is described as sudden in onset, constant, and not affected by movement or position. Occasionally, there is radiation to the legs, buttocks, or groin.
- (2) Findings consistent with shock (hypotension, pallor, diaphoresis, oliguria, and obtundation) can develop rapidly with a ruptured aneurysm.

b. **Physical findings**

- (1) A palpable, pulsatile mass may be felt on abdominal examination and may extend variably from the xiphoid process to below the umbilicus, although accurate sizing is nearly impossible on physical examination. Palpation should be gentle or potentially avoided, especially if the aneurysm is tender, as tenderness can be an indication of impending rupture.
- (2) Associated vascular disease is common among those with AAA and may be represented by abdominal or femoral bruits or decreased pulses in the extremities.
- (3) Examination findings of distal thromboembolism may be noted in the distal extremities and represent atheromatous material or mural

thrombus with embolism. Other related findings may include livedo reticularis, painful blue toes, hypertension, and acute kidney injury.

4. Diagnostic testing

- a. **Abdominal ultrasound** is the most commonly used screening tool for AAA. Aortic ultrasound has the capacity to obtain both longitudinal and transverse images of the aneurysm and has been validated to accurately measure size to within ± 0.3 cm. **Major advantages of ultrasound include its wide availability, cost-effectiveness as a diagnostic and screening imaging technique, and avoidance of ionizing radiation exposure.** If imaging is adequate, ultrasound is an effective option when monitoring aneurysm growth serially. Disadvantages of abdominal ultrasound include poor definition of branch vessels; therefore, ultrasound is insufficient for preoperative evaluation.
- b. **CT aortography** with cardiac gating allows for accurate evaluation of the aneurysm shape, and volumetric acquisition provides detailed three-dimensional analysis of spatial relations to branch vessels and diagnosis of associated acute aortopathies including PAU. CT measurements have been validated to within ± 0.2 cm. CT offers an advantage of evaluating for extravasated blood in acute or subacute rupture. The major disadvantages of CT include the requirement for ionizing radiation and intravenous contrast, which limit its utility in follow-up of chronic aortic dissection (see Chapter 52).
- c. **MRI** provides excellent definition of aneurysm size as well as suprarenal and iliofemoral extension. MRA allows for improved visualization of compromised flow to branch vessels, although it lacks sensitivity to absolutely define obstruction in the renal vessels. MRI is disadvantaged by cost and limited availability.
- d. **Aortography** effectively defines both suprarenal and iliofemoral involvement as well as branch vessel impingement, although it tends to underestimate the size, especially when mural thrombus is present. Compared with other techniques, aortography is invasive and requires the use of intravenous contrast and ionizing radiation. Aortography is now generally reserved for planning endografting in some centers and is less useful as an initial diagnostic modality.

5. Therapy

a. Medical therapy

- (1) β -Blockers have been shown to decrease the rate of enlargement and risk of rupture in at least one clinical trial (Gadowski et al., *J Vasc Surg.* 1994), although other studies have not confirmed this effect.
- (2) Aggressive risk factor modification with control of hypertension and hypercholesterolemia is **imperative to prevent adverse events from atherosclerotic disease in other vascular beds. Smoking cessation should be strongly advocated.**
- (3) Serial ultrasound or CT scanning is indicated in patients without symptoms that have aortic diameters of 2.5 cm or greater. Studies should be obtained yearly when the aortic diameter reaches 3.0 cm, every 6 months for dimensions between 4 and 5 cm, and every 3 to 6 months for aneurysms between 5.0 and 5.5 cm not surgically repaired. Ultrasound is generally preferred for surveillance of small AAAs, owing to lack of radiation exposure.

- b. **Endovascular aortic repair.** Percutaneous aortic stent-grafting has been FDA-approved for use in descending thoracic aortic or infrarenal AAA. Endovascular grafting is a less invasive option for the repair of AAA and is especially appealing for elderly patients or those with substantial cardiac, pulmonary, and renal dysfunction.

- (1) **The EVAR procedure.** Under fluoroscopic guidance, the proximal and distal ends of the stent-graft are affixed to normal segments of the aorta above and below the aneurysmal portion, thereby sealing off the

aneurysm. **Suitable anatomy is necessary for stent-grafting.** Favorable characteristics for EVAR include normal diameter of aorta distal to the renal arteries and proximal to the aneurysmal segment, minimal angulation, freedom from severe obstructive lesions, and patency of side branches and distal iliac vessels. Only 30% to 60% of patients will have anatomy suitable for endovascular repair.

- (2) **Comparing EVAR with open surgical repair.** Several randomized trials have compared endovascular repair with open surgical repair, including the Dutch Randomized Endovascular Aneurysm Management (DREAM) trial, the Endovascular Aneurysm Repair 1 (EVAR-1) trial, and the Open Versus Endovascular Repair (OVER) Veterans Affairs Cooperative trial, among others. Six years after randomization, patients in the DREAM trial received no survival benefit after EVAR compared with those undergoing conventional surgery. Similarly, patients followed to a median of 6 years in the EVAR-1 trial enjoyed a lower operative mortality with endovascular repair over open repair, although no differences were seen in total mortality or aneurysm-related mortality in the long term. As techniques improve, so too may postoperative outcomes among patients randomized to endovascular versus open AAA repair. An interim report from the most contemporary OVER Veterans Affairs Cooperative trial has concluded that early operative advantages of EVAR have not yet been offset by increased morbidity and mortality in the first 2 years after aortic repair. Further comparisons of outcome data from this and other ongoing trials will continue to provide appraisal of the long-term clinical benefits and cost-effectiveness of this technique compared with conventional therapy.
- (3) **EVAR among unsuitable surgical candidates.** Compassionate use of EVAR among patients for whom open repair is deemed too high risk because of medical comorbidities was studied in the Endovascular Aneurysm Repair 2 (EVAR-2) trial. This study failed to show any survival benefit with endovascular repair—a disappointing finding as the clearest indication for endovascular repair was traditionally thought to be for those at high risk for open repair.
- (4) **Endoleak as a complication of EVAR.** One of the common complications of endovascular repair is endoleak (Table 26.5). Endoleak represents a failure of the stent-graft to completely exclude the aneurysm and

TABLE 26.5 **Classification of Endoleaks**

Endoleak type	Cause of leak about graft
I	Inadequate seal at proximal and/or distal graft attachment
II	Retrograde arterial flow into the aneurysm sac from an aortic arterial branch within the stented segment
III	Structural failure of the graft material (e.g., graft tear or hole, stent fracture)
IV	Stent-graft porosity
V	Aneurysmal expansion without demonstrable endoleak (“endotension”)

Modified from Hiratzka, LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease. *J Am Coll Cardiol.* 2010;55(14):e27–e129.

results in persistent flow into the aneurysm, thereby increasing the risk of aneurysm expansion and rupture. Endoleaks occur in 10% to 20% of cases and are associated with more frequent reinterventions than open repair and the requirement of lifelong periodic follow-up imaging.

- (5) **Other complications related to EVAR** include endograft migration, prosthesis infection, vascular access site-related infections, bleeding, thromboembolism, and spinal cord ischemia with paraplegia.
 - (6) *Periodic long-term surveillance imaging should be performed to monitor for endoleak, confirm graft position, document shrinkage or stability of the excluded aneurysm sac, and determine the need for further intervention in patients who have undergone endovascular repair of infrarenal aortic and/or iliac aneurysms (Level of Evidence: A).*
- c. **Surgical therapy.** Surgical repair generally requires resection of the aneurysmal segment, with replacement using a Dacron tube graft inserted in place of the diseased aorta. The major branches are then reimplanted to the graft.
- (1) **Preoperative evaluation.** Given the strong association of coronary artery disease with AAA and high operative mortality with untreated severe coronary artery disease, **all patients being considered for surgical repair of AAA require preoperative cardiac risk assessment.** Perioperative mortality in elective procedures is 4% to 6% (< 2% in low-risk patients).
 - (2) **Repair of AAAs < 5.0 cm in diameter provides no long-term survival benefit.** Controversy remains regarding medical versus surgical management of aneurysms between 5.0 and 5.5 cm and so should be managed on a case-by-case basis. **Surgery is indicated for an aneurysm with diameter measuring 5.5 cm or if rapidly expanding (> 1 cm/y).** Women have a higher overall risk of rupture and tend to rupture at smaller aortic diameters compared with males. Therefore, it is the recommendation of some vascular societies that women should undergo elective repair at aortic diameters 4.5 to 5.0 cm. Symptomatic patients should also be referred for repair.
- B. **Thoracic aortic aneurysm.** Thoracic aneurysms include those that involve the aorta from the level of the aortic root to the diaphragmatic crura. Extension of a descending thoracic aneurysm below the diaphragm creates a thoracoabdominal aneurysm.
1. **Clinical presentation.** Most patients with thoracic aneurysm are asymptomatic at the time of diagnosis, and the condition is often discovered as an incidental finding on imaging done for other reasons.
 - a. **Signs and symptoms**
 - (1) **Vascular complications of the aneurysm** include AI with left ventricular dilatation and CHF, myocardial ischemia due to coronary artery compression, sinus of Valsalva rupture into the right atrium/ventricle with left-to-right shunt and CHF, or thromboembolic phenomena.
 - (2) **Compression of external structures by the aneurysm** causes superior vena cava syndrome, dysphagia from esophageal compression, or hoarseness from recurrent laryngeal nerve compression. In addition, compression of the trachea or mainstem bronchus can lead to wheezing, dyspnea, tracheal shift, cough, or hemoptysis. Chest or back pain from compression and bony involvement is described as constant, boring, and deep.
 - (3) **Rupture** presents with sudden, severe, sharp chest or back pain. In order of decreasing frequency, TAAs rupture into the left pleural space, the pericardium (presenting as tamponade), and the esophagus (presenting as hematemesis).
 - (4) **Aortic dissection.** See Section III.

- b. Physical examination. Specific physical findings directly attributable to TAA **are usually absent**.
 - (1) **Cardiac**. The diastolic murmur of AI (classically right lower sternal border) and a laterally displaced point of maximum impulse are sometimes noted with chronic ascending aortic dilatation. Signs of CHF can be seen in these circumstances. Unilateral jugular venous distention can be seen in patients with venous compression.
 - (2) **Vascular**. Rarely, a pulsatile mass can be palpated in the suprasternal notch. Differential pulses in the extremities can sometimes be found. Evidence of thromboembolic events can be seen upon examination of the digits. If the aneurysm compresses the venous return, evidence of superior vena cava syndrome or lower extremity edema may be found.
 - (3) **Pulmonary**. If the aneurysm compresses part of the bronchial tree, decreased air movement or stridor is auscultated.
- 2. **Etiology**
 - a. Table 26.6 gives the various classifications of TAAs as well as the segment involved and pathophysiology. The most common cause of TAA formation is medial necrosis, characterized by loss of elastic fibers and smooth muscle within the aortic media with replacement of tissue with interstitial cysts of basophilic ground substance leading to a cystic appearance.
 - b. Approximately 5% to 10% of patients undergoing surgery for AI are secondary to **annuloaortic ectasia**, which is a variant of cystic medial necrosis. Annuloaortic ectasia is a clinicopathologic diagnosis in which the aortic root, ascending aorta, and aortic annulus dilate, resulting in AI. This is more common in men and is typically seen in the fourth, fifth, and sixth decades of life.
- 3. **Clinical course and surgical recommendations for asymptomatic TAA**
 - a. Onset of symptoms usually heralds a more rapid course, as do larger dimensions at baseline. *Patients with symptoms suggestive of expansion of a TAA should be evaluated for prompt surgical intervention unless life expectancy from comorbid conditions is limited or quality of life is substantially impaired (Level of Evidence: C).*
 - b. Rupture is the most common cause of death in these patients. Data from the Yale group found that median size at rupture for an ascending aortic aneurysm was 6.0 cm and for a descending aortic aneurysm it was 7.2 cm. ***Asymptomatic patients should be evaluated for surgical repair who have degenerative TAA, IMH, PAU, mycotic aneurysm, or pseudoaneurysm, who are otherwise suitable candidates and for whom the ascending aorta or diameter of the aortic sinuses is 5.5 cm or greater (Level of Evidence: C).***
 - c. TAAs tend to grow more rapidly as they increase in size and thereby increase the risk of acute rupture or dissection. Aneurysms < 5.0 cm at baseline have a mean growth rate of 0.17 cm/y, whereas those > 5.0 cm grew at a mean rate of 0.79 cm/y. ***Patients with a growth rate > 0.5 cm/y in an aorta that is < 5.5 cm in diameter should be considered for operation (Level of Evidence: C).***
 - d. ***Patients undergoing aortic valve repair or replacement who also have an ascending aorta or aortic root diameter > 4.5 cm should be considered for concomitant repair of the aortic root or replacement of the ascending aorta (Level of Evidence: C).***
 - e. ***Patients with Marfan, Loeys-Dietz, or vascular-type Ehlers-Danlos syndrome or other genetically mediated disorders (BAV, Turner syndrome, and familial TAA and dissection) should undergo elective operation at smaller diameters (4.0 to 5.0 cm depending on the condition) to avoid acute dissection or rupture (Level of Evidence: C).*** Among patients with Marfan syndrome and BAV, the ratio of maximal aortic cross-sectional area in square centimeters to the patient's height in meters with a result of > 10 has been proposed as

TABLE 26.6 Causes of Thoracic Aortic Aneurysm

Etiology	Aortic segment involved	Pathophysiology
Cystic medial degeneration	Ascending aorta, aortic arch	De novo cystic medial degeneration
Marfan syndrome	Ascending aorta and root, aortic arch	Defective fibrillin; secondary cystic medial degeneration
Loeys-Dietz syndrome	Aortic root aneurysms (98%) and arterial tortuosity, especially of the head and neck vessels	Autosomal dominant; defective transforming growth factor receptor type I or II genes
Ehlers-Danlos syndrome, type IV	Ascending aorta, predominantly aortic arch	Defective collagen; secondary cystic medial degeneration
Bicuspid aortic valve	Ascending aorta and root	Inadequate production of fibrillin; cystic medial degeneration
Familial thoracic aortic aneurysm syndrome	Ascending aorta	Autosomal dominant, 3p24.2-25, 5q13-15, 11q23.2-q24
Turner syndrome	Ascending aorta and root	Cystic medial degeneration
Advanced age		Cystic medial degeneration
Atherosclerotic	Descending aorta	Atherosclerotic plaques, weakening vessel walls
Traumatic	Aortic isthmus, proximal descending aorta	Damaged vessel wall, intramural hematoma
Inflammatory	Variable	Takayasu arteritis, giant cell arteritis, HLA-B27–associated spondyloarthropathies, others
Infectious	Aortic root (syphilis), variable (mycotic)	Cystic medial degeneration (syphilis), inflammatory changes (mycotic)
Poststenotic	Ascending (aortic stenosis), descending (coarctation)	Hemodynamic insult
Postsurgical	Aortic valve replacement, status post–aortic anastomosis	Weakening of the anastomotic walls
Chronic aortic dissection	Variable	Weakening of false lumen over time

an indication for surgical intervention, particularly since patients with this finding may be at greater risk for spontaneous dissection.

4. **Diagnostic testing.** Unique advantages and disadvantages of each radiographic technique are described in detail in preceding sections. The specific attributes of each technique when evaluating TAA are reviewed below.

- a. The **chest radiograph** frequently shows widening of the mediastinum, unusual aortic contours, or displacement of the trachea or bronchi in the presence of a large TAA.

- b. Both computed tomography angiography (CTA) and MRA provide excellent assessment of size and extent of aneurysmal involvement. CTA is the preferred modality for serial follow-up after surgical or endovascular repair, whereas MRA is the preferred modality when visualization of the aortic root is necessary.
 - c. **TTE and TEE.** TTE is of limited use in evaluating the thoracic aorta, except for the aortic root and proximal ascending portion. TEE can be used to visualize the entire thoracic aorta, but given the availability of noninvasive imaging to diagnose TAA, TEE is not routinely used for this purpose.
 - d. MRI and MRA are also useful for detecting and defining the extent of aneurysmal involvement. They allow for evaluation of the entire aorta, branch vessels, aortic valve, and pericardium.
 - e. Aortography allows for evaluation of the segment involved by the aneurysm as well as the branch vessels off the aorta. This procedure is currently reserved for preoperative evaluation to establish branch vessel patency.
5. **Therapy**
- a. **Medical therapy.** Long-term data on medical management for TAA are lacking. Based on one small prospective trial of patients with Marfan syndrome, patients treated with propranolol enjoyed a slower rate of aortic dilatation. *β -Blockers are generally recommended for all patients with TAA, but particularly those with Marfan syndrome to reduce the risk of aortic dilatation (Level of Evidence: B). Antihypertensive therapy should be administered to hypertensive patients with TAA to achieve a goal blood pressure < 140/90 mm Hg, or < 130/80 mm Hg among patients with concurrent diabetes mellitus or chronic kidney disease (Level of Evidence: B). The angiotensin receptor blocker losartan may be particularly beneficial to slow aneurysm growth in patients with Marfan syndrome (class IIa, Level of Evidence: B).* Losartan has been shown in animal models of Marfan syndrome to slow the rate of dilatation of the aorta and human studies are underway.
 - b. **Endovascular therapy.** Use of percutaneous aortic stent-grafts has been reported in aortic arch and descending thoracic aneurysms. Contemporary studies, including the Talent VALOR and Zenith TX2 trials, have suggested that endovascular therapy represents a safe and effective strategy and an alternative to open surgery in patients with TAA. However, these studies have also exposed limitations of EVAR including restricted applicability due to a need for careful patient selection with anatomy appropriate for endovascular techniques, vascular access and device implantation issues, and need for concomitant subclavian and less commonly carotid artery bypass grafting, among others. Larger studies and longer follow-up must be presented before widespread use of this technology can be encouraged. Currently, EVAR is reserved for TAA among patients at high risk for open repair among those with ideal aortic anatomy having the procedure performed in centers with a qualified team to perform open aortic surgery.
 - c. **Preoperative evaluation for TAA**
 - (1) *In preparation for surgery, imaging studies adequate to establish the extent of disease and the potential limits of the planned procedure are recommended (Level of Evidence: C).*
 - (2) *Patients with thoracic aortic disease requiring a surgical or catheter-based intervention who have symptoms of myocardial ischemia should undergo additional studies to determine the presence of significant coronary artery disease (Level of Evidence: C). Patients with unstable coronary syndromes and significant coronary artery disease should undergo preoperative revascularization or concomitant coronary artery bypass graft surgery (Level of Evidence: C).*

d. **Surgical therapy for TAA.** The technical details of repair are beyond the scope of this text. However, the basic premise is for a Dacron tube graft to be inserted in place of the diseased aorta. The main branches are reimplanted to the graft (coronary arteries, great vessels, mesenteric, and T₈ to L₂ intercostals/lumbricals). When the aortic valve is involved with aortic root dilatation, a modified **Bentall procedure** (composite prosthetic aortic valve with Dacron graft) or **aortic valve homograft** is performed. The aortic valve homograft is a cryopreserved cadaveric aortic valve with a portion of the original ascending aorta intact. Aneurysms involving both the ascending and descending aorta can be treated by a two-staged approach, with an **elephant trunk** procedure. With this, the ascending aorta and arch are replaced initially and the distal portion of the graft is suspended into the proximal portion of the descending thoracic aorta for subsequent union with a descending aorta graft placed either by open surgical procedure or percutaneously. Overall perioperative survival is reported to be 90% to 95% for elective repair (ascending aorta) in most institutions.

- (1) *Patients with Marfan, Loays-Dietz, and Ehlers-Danlos syndromes and other patients with dilatation of the aortic root and sinuses of Valsalva should undergo excision of the sinuses in combination with a modified valve-sparing root reimplantation (David) operation if technically feasible or, if not, root replacement with valved graft conduit (Level of Evidence: B).*
 - (2) *For patients with degenerative or traumatic aneurysms of the descending thoracic aorta exceeding 5.5 cm, saccular aneurysms, or postoperative pseudoaneurysms, endovascular stent-grafting should be strongly considered if feasible (Level of Evidence: B).*
 - (3) *For patients with thoracoabdominal aneurysms, in whom endovascular stent-graft options are limited and surgical morbidity is elevated, elective surgery is recommended if the aortic diameter exceeds 6.0 cm, or less if a connective tissue disorder such as Marfan or Loays-Dietz syndrome is present (Level of Evidence: C).*
 - (4) *For patients with thoracoabdominal aneurysms and with end-organ ischemia or significant stenosis from atherosclerotic visceral artery disease, an additional revascularization procedure is recommended (Level of Evidence: B).*
- e. **Complications after TAA repair.** These include MI (7.2%), CVA (4.8%), acute renal failure (2.4%), perioperative hemorrhage (7.2%), and paraplegia (6.0%) due to perioperative ischemia of the anterior spinal cord. Procedural adjuncts, including epidural cooling, distal aortic perfusion to support collateral circulation to the spinal cord during surgery, and motor-evoked potential monitoring, have been used to reduce the rate of paraplegia.
- (1) Factors associated with increased surgical risk include emergent surgery, greater age, prolonged cross-clamp time, diabetes, previous aortic surgery, and intraoperative hypotension.

IV. CONTROVERSIES AND FUTURE RESEARCH DIRECTIONS

- A. **Screening for AAA.** The U.S. Preventive Services Task Force (USPSTF) currently recommends one-time screening for AAA by ultrasound in men aged 65 to 70 years who have ever smoked, although it makes no recommendation for screening of men that have never smoked. What's more, the USPSTF recommends against routine screening for AAA in women. These recommendations are based on a systematic review of four large randomized trials of screening for AAA, with ultrasound beneficial among ever-smoking men aged 65 to 79 years alone. Further investigation is needed to refine the concept of screening for AAA, particularly in women.
- B. **Risks and Benefits of Imaging Technologies.** Compared with acute coronary syndromes, acute aortic syndromes are less common, although several features of

each disease overlap. When acute aortic disease is suspected, rapid and accurate assessment is required so as to avoid delays in treatment of acute coronary syndromes, as suggested by ECG. What's more, imaging techniques used for aortic disease requiring longitudinal follow-up must be cost-effective and avoid unnecessary radiation exposure. Clinical studies exploring cost-effectiveness and safety of various screening protocols are needed.

- C. Clinical Therapeutic Trials for Aortic Syndromes.** The National Heart, Lung, and Blood Institute has recommended an Aortic Aneurysm Clinical Trials Network be developed to test medical and surgical treatments among patients with TAA. Significant interest and efforts are underway to develop novel therapeutic targets and biomarkers for acute aortic dissection using animal models. Gene-based models that describe mechanisms of aortic disease based on specific mutations have contributed greatly to our understanding of Marfan, Loeys-Dietz, and other familial syndromes. Further collaborative efforts and expansion of existing registries are likely to improve understanding and provide more effective treatments for diseases of the aorta.

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CHAPTER

27

Femi Philip

Peripheral Arterial Disease

I. INTRODUCTION. Peripheral arterial disease (PAD) describes the pathologic states that lead to stenoses and aneurysms in the noncoronary arterial circulation. This chapter focuses on the diseases of the **arterial supply to the extremities** and the **renal vasculature** (disease states involving the aorta and cerebral vasculature are discussed elsewhere in this volume). PAD can be classified as occlusive or aneurysmal. **Atherosclerosis is the most common cause of PAD.** In **aneurysmal** states, weakening of the arterial media results in focal dilatation of the artery to at least 1.5 times the normal diameter. These aneurysmal segments can subsequently dissect, rupture, or thrombose, with catastrophic consequences. In addition to atherosclerosis, there are several less common pathologies that can cause PAD, including vasculitis, arterial injury, entrapment syndromes, and cystic adventitial disease. These disorders are beyond the scope of this chapter.

II. LOWER EXTREMITY PERIPHERAL ARTERY DISEASE

A. Etiology and natural history. Atherosclerosis is the most common cause of lower extremity PAD. Traditional risk factors include age, smoking history, diabetes mellitus, hyperlipidemia, and hypertension. Emerging risk factors include elevated

markers of inflammation such as C-reactive protein, fibrinogen, and interleukin 6; chronic kidney disease; hypercoagulable states such as hyperhomocysteinemia; and possibly a genetic predisposition to PAD. African Americans have a twofold increase in risk of developing PAD. The prevalence of PAD increases significantly with age, such that the prevalence is 2% to 3% in persons aged ≤ 50 years and up to 20% in persons aged > 70 years. **Fibromuscular dysplasia (FMD)**, a noninflammatory and nonatherosclerotic process, can also affect the lower extremities by causing hyperplastic cell growth and luminal narrowing, although it predominantly affects the renal and carotid arteries. Patients with lower extremity PAD may present with leg symptoms or may be entirely asymptomatic. Approximately 50% of patients > 55 years old with PAD, with or without claudication symptoms, when followed for 5 years will remain stable or improve with exercise and lifestyle modifications. The remaining 50% will have progressive worsening of symptoms, and approximately 4% will require major amputation if they do not undergo revascularization. The highest risk of amputation occurs in those patients who are diabetic and continue to smoke. **Cardiac disease accounts for the majority of deaths in patients with PAD, in whom the relative risk of death from cardiac causes is increased more than sixfold. Approximately one-third to one-half of all patients with PAD will have concomitant coronary disease depending on the diagnostic criteria utilized, and thus PAD is considered a coronary artery disease risk equivalent.**

B. Clinical manifestations

1. **Signs and symptoms.** Rest perfusion of the lower extremities may be adequate; however, if the arterial stenosis is severe, then exercise may precipitate ischemia and **claudication**. Symptoms may include pain, discomfort, or fatigue of the buttock, thigh, or calf musculature and are usually gradual in onset. The amount of exercise required to precipitate pain is roughly related to the severity of the stenosis. Pain is usually manifested one segment below the area of severe stenosis (Table 27.1), and the most frequently involved artery in intermittent claudication is the superficial femoral artery. The symptoms are usually promptly relieved with rest or standing. More severe stenosis or more distal atherosclerotic lesions may result in **limb-threatening ischemia with foot pain at rest, tissue ulceration, or gangrene**. There are two terms frequently used to describe this condition that should be differentiated: critical limb ischemia and acute limb ischemia. **Critical limb ischemia** is resting limb pain that results from severe atherosclerotic disease that compromises distal blood flow of the involved limb. This term is typically used to describe chronic lesions such as ischemic rest pain, ischemic ulcers, or gangrene and is caused by a slow progression of atherosclerotic disease. **Acute limb ischemia** occurs abruptly and threatens the viability of the involved tissue. Acute limb ischemia is usually the result of an embolic event or arterial thrombosis.
2. **Physical examination.** Characterization of **femoral, popliteal, dorsalis pedis, and posterior tibial pulses; auscultation for bruits** in the abdomen and

TABLE 27.1 Localization of Peripheral Arterial Disease

Location of pain	Likely involved segment
Buttock and thigh	Aortoiliac
Thigh	Aortoiliac, common and/or profunda femoral artery
Calf	Superficial femoral or popliteal artery ^a
Foot	Tibial or peroneal arteries

^aMost commonly involved artery.

bilateral groins; and palpation for **aneurysm** in the abdomen and over the popliteal arteries are all part of a comprehensive lower extremity vascular examination. A complete cardiac examination and auscultation of carotid arteries should also be performed to assess for concurrent abnormalities, given the common atherosclerotic pathogenesis of cerebral, myocardial, and peripheral arterial disease. Signs of lower extremity arterial insufficiency can include coolness, dry skin and scaling, pallor that is worsened with leg elevation, and ulcerations. Rarely muscular atrophy can be seen. The evaluation of a patient with possible acute limb ischemia should include the “5 P’s”: pain, pallor, pulselessness, paresthesias, and paralysis. These clinical features have prognostic value in acute limb ischemia (Table 27.2).

C. Diagnostic evaluation (Fig. 27.1)

1. **Ankle-brachial index (ABI).** The ABI is a measurement of lower extremity perfusion, which compares the blood pressure in a pedal artery with the higher of two brachial artery blood pressures. The ABI cannot localize stenosis, but is a simple and accurate measure of disease severity (Table 27.3). In general, ABI value correlates poorly with symptoms, and two patients with the same ABI may have remarkably different complaints. **Symptoms at rest rarely occur, unless the ABI is < 0.4 (i.e., critical limb ischemia).** The ABI has limited use in noncompressible, calcified vessels. In patients with noncompressible ankle vessels (ABI > 1.4) the toe-brachial index can be used in conjunction with pulse-volume recordings (PVRs) to document PAD. Measuring the ABIs before and after exercise can help diagnose PAD when the resting ABI is normal but there is a high clinical suspicion for PAD. It can also help differentiate between true claudication and nonarterial leg pain (pseudoclaudication).
2. **Pulse-volume recordings.** PVRs detect changes in the volume (arterial flow) of the limb during the cardiac cycle. Blood pressure cuffs are placed at the thigh (one or two cuffs), calf, ankle, midfoot, and toe. The change in volume of the respective cuff during the cardiac cycle identifies the presence of arterial stenosis by reduction in the pulsatile flow as detected by changes in pulse contour and amplitude at that cuff, as documented by the PVR waveform (Fig. 27.2). Segmental blood pressure measurements may be taken along the leg with the segmental PVR tracings for localization of disease. Unlike ABIs, arterial

TABLE 27.2 **Categorizing Acute Limb Ischemia**

Category	Prognosis	Sensory loss	Muscle weakness	Arterial Doppler signal	Venous Doppler signal
Viable	Not immediately threatened	None	None	Audible	Audible
Threatened marginally	Salvageable if promptly treated	Minimal (toes) or none	None	Often inaudible	Audible
Threatened immediately	Salvageable with immediate revascularization	More than toes, rest pain	Mild, moderate	Usually inaudible	Audible
Irreversible	Major tissue loss or permanent nerve damage	Profound anesthesia	Profound paralysis	Inaudible	Inaudible

Adapted from Katzen BT. Clinical diagnosis and prognosis of acute limb ischemia. *Rev Cardiovasc Med.* 2002;3(suppl 2):S2–S6.

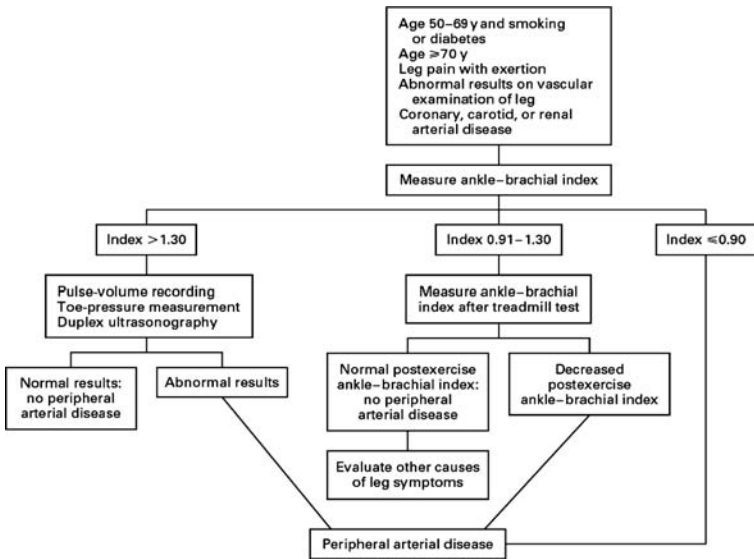


FIGURE 27.1 Evaluation of patients in whom peripheral arterial disease is suspected. (Reproduced from Hiaat WR. Medical treatment of peripheral arterial disease and claudication. *N Engl J Med.* 2001;344:1608, with permission.)

calcification does not effect PVR tracings, and PVR can often be helpful in the diabetic patient with a foot ulcer and suspected arterial calcification.

3. **Duplex ultrasound.** Arterial duplex renders an anatomic assessment of the arterial system using a combination of B-mode ultrasound imaging and Doppler frequency spectral analysis. Doppler complements the standard qualitative ultrasound imaging by allowing waveform analysis and assessment of Doppler velocities. Using the concept that velocity of blood flow increases as it flows through a stenotic lesion, peak systolic and end-diastolic velocities are measured and used to estimate the severity of a stenosis. This modality is useful for anatomic visualization of lesions and for surveillance after stenting or bypass grafting.

TABLE 27.3 Evaluating Disease Severity with the Ankle–Brachial Index

ABI	Interpretation
1.3	Noncompressible vessel
1.0–1.29	Normal
0.91–0.99	Equivocal
0.4–0.90	Mild to moderate PAD
< 0.4	Severe PAD

ABI, ankle–brachial index.

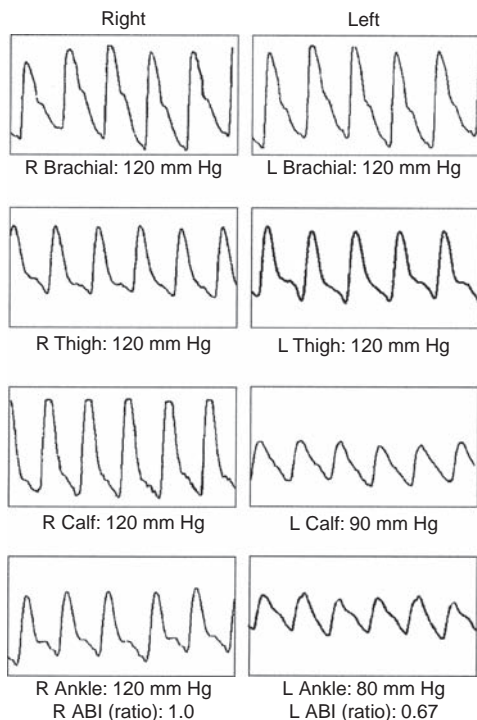


FIGURE 27.2 Pulse-volume recording (PVR) of the lower extremities. This PVR was obtained from a 42-year-old man with a history of diabetes mellitus and tobacco use who developed new left calf cramping with exertion. It demonstrates moderate disease (ankle-brachial index [ABI] = 0.66) of left femoropopliteal segment and a normal recording on the right lower extremity. He was advised to begin both a tobacco cessation program and a walking regimen.

4. **Magnetic resonance angiography (MRA).** The MRA signal is a reflection of the velocity and flow patterns of protons within the artery. The noninvasive nature of MRA and its ability to generate three-dimensional (3D) reconstructions are the main advantages of MRA over conventional angiography. Its limitations include a tendency to overestimate lesion severity secondary to flow turbulence, imaging artifact with metal clips or stents, and its association with nephrogenic systemic fibrosis (2.5% to 5.0%) in patients with a glomerular filtration rate < 30 mL/min. Despite these limitations, MRA still has a class I indication to diagnose the anatomic location and severity of stenosis in patients with PAD.
5. **Computed tomographic angiography (CTA).** CTA is a rapidly progressing technology that uses an intravenous contrast agent and a multidetector scanner to obtain images that are of similar quality to those of conventional angiography. A total of 64 detector scanners allow the simultaneous acquisition of 64 cross-sectional image slices; this has dramatically reduced radiation and contrast doses required to obtain adequate images. CTA has the advantage of being capable of reconstructing 3D images in virtually any oblique projection to help evaluate

eccentric stenoses. Other advantages of CTA include better visualization of collaterals to distal vessels, identification of aneurysms, and cystic adventitial disease, which may not be picked up by conventional angiography. CTA also has several disadvantages when compared with catheter-based angiography: CTA has lower spatial resolution than digital subtraction, venous opacification can interfere with visualization of arterial filling, asymmetric leg filling may miss the arterial phase in some vessels, and the enormous quantity of data obtained (up to 2,000 images) may be difficult for workstations to process and store. Several recent studies have shown the accuracy of CTA for the diagnosis of stenoses > 50%, and CTA is quickly becoming an important imaging modality for the diagnosis of PAD. Currently, the American College of Cardiology/American Heart Association (ACC/AHA) PAD guidelines give a class IIb indication for CTA in the diagnosis of the anatomic location and severity of stenosis in patients with PAD.

6. **Catheter-based angiography.** Long considered the gold standard for the diagnosis of arterial disease, this invasive procedure requires intraarterial vascular access and contrast (often nonionic dye, although gadolinium or carbon dioxide can be used). It is recommended for the evaluation of patients for whom revascularization procedures are planned (those with lifestyle-limiting claudication, rest pain, ischemic ulceration, or gangrene) or for whom noninvasive techniques are inconclusive. Because contrast angiography demonstrates only the arterial lumen, it can underestimate lesion severity. Contrast angiography (Ia) with digital subtraction (Ib) has a class I indication for patients with PAD when revascularization is considered.

D. Treatment. The two main goals of therapy for patients with PAD are to relieve symptoms and improve survival from related cardiovascular diseases. Options for treatment of intermittent claudication include surgical revascularization (“bypass”), percutaneous revascularization, pharmacotherapy, and exercise. Aggressive risk factor modification is the primary therapy for the prevention of cardiovascular events. Therefore, the mainstay of treatment for many patients with mild to moderate claudication is to **“stop smoking and start walking.”** Accordingly, a trial of supervised exercise therapy is given a class I recommendation as the initial therapy of choice for claudication in the ACC/AHA PAD guidelines. Supervised exercise therapy (“PAD rehab”) has been reported to increase walking distance by up to 130% to 180% among patients with claudication.

1. Antiplatelet therapy

Aspirin/clopidogrel. Current guidelines recommend that all PAD patients should be on aspirin (75 to 325 mg) therapy unless contraindicated (class I). Clopidogrel can be used in the setting of aspirin allergy (class I). In a subset analysis of the Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial, clopidogrel reduced composite major adverse events by 23.8% compared with aspirin in a large cohort of 19,185 patients with atherosclerotic vascular disease, of whom 6,452 had symptomatic PAD. In terms of dual antiplatelet therapy, the Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events (CHARISMA) trial failed to show a significant additive reduction in composite cardiovascular events with dual antiplatelet therapy in patients with asymptomatic cardiovascular disease or multiple cardiovascular disease risk factors but did show a reduction in myocardial infarction and hospitalization in a subset of PAD patients, albeit at the cost of higher rates of bleeding.

Since the publication of the guidelines, several recent trials have triggered some debate about the efficacy of aspirin for prevention of cardiovascular events in patient with PAD. The Prevention of Progression of Arterial Disease and Diabetes (POPADAD) trial comprising 1,276 patients with diabetes and $ABI \leq 0.99$ showed that aspirin failed to prevent the composite cardiovascular end point when compared with placebo (hazard ratio [HR] 0.98; 95% confidence interval [CI] 0.76 to

1.26). The Aspirin for Asymptomatic Atherosclerosis (AAA) trial comprising 3,350 patients with $ABI \leq 0.95$ and no known cardiovascular disease also showed a failure of aspirin to decrease rates of composite cardiovascular events when compared with placebo (HR 1.03; 95% CI 0.84 to 1.27). A meta-analysis of randomized controlled trials including 18 trials and 5,269 patients showed that while there is a trend for aspirin to prevent cardiovascular events, the difference is not statistically significant (risk ratio [RR] 0.88; 95% CI 0.76 to 1.04). In light of these recent trial data, recommendations from updated PAD guidelines are eagerly anticipated.

2. Risk factor modification. PAD is a coronary risk equivalent and as such aggressive risk factor modification is warranted.

- a. Cigarette **smoking** has been associated with progression of atherosclerosis. Physician counseling is essential, as **tobacco cessation can reduce the 5-year amputation risk and decrease the 5-year mortality rate by 50%**. The importance of this intervention cannot be underestimated. Whenever possible, extensive counseling and referral to formal smoking cessation programs should be offered (class I). In addition, several pharmacologic therapies are available (bupropion, nicotine replacement, and varenicline) and should be prescribed when indicated.
- b. Current guidelines recommend treatment of **hypertension** to goal blood pressure $< 140/90$ mm Hg in patients with PAD and $< 130/80$ mm Hg in patients with PAD and diabetes or chronic kidney disease to prevent the development of future cardiovascular adverse events. The use of β -blockers as antihypertensive agents in patients with PAD is *not* contraindicated. Given the findings of the Heart Outcomes Prevention Evaluation Study, which included patients with PAD, it is reasonable to treat patients with symptomatic PAD, irrespective of diabetes, with an angiotensin-converting enzyme (ACE) inhibitor to reduce cardiovascular events (class IIa).
- c. Aggressive treatment of **hyperlipidemia** should include therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) whenever possible to achieve a low-density lipoprotein (LDL) goal of < 100 mg/dL in patients with PAD (class I). For patients at especially high risk for ischemic events, an LDL goal of < 70 mg/dL may be desirable (class IIa). Patients with normal LDL cholesterol, low high-density lipoprotein (HDL) cholesterol, and elevated triglycerides may derive benefit from a fibric acid derivative (class IIa).
- d. The management of **diabetes** in patients with PAD is important, given their increased risk of amputation (overall 20%) and increased mortality (estimated to be 50% at 5 years). Current recommendations advocate daily assessment of the feet to aid in the early identification of complications of ischemia, such as foot ulcers (class I). The recommended target HbA1c is $< 7.0\%$ (class IIa). Aggressive risk factor modification is a critical component of management for diabetic patients with PAD, and these patients should be treated with antiplatelet therapy, lipid-lowering agents, and ACE inhibitors in the absence of contraindication.

3. Treatment of claudication

- a. **Exercise is an inexpensive, low-risk option in comparison with invasive therapies and pharmacotherapies for intermittent claudication.** Potential mechanisms by which exercise improves symptoms include augmentation of collateral flow, improved rheologic characteristics of blood, decreased reliance on anaerobic metabolism, and greater extraction of oxygen. Supervised exercise programs have been shown to improve pain-free walking distance up to 180% from resting values. For patients with symptomatic claudication, current guidelines recommend a supervised exercise program for 30 to 45 minutes three times a week for at least 12 weeks (class I). For patients who do not have a supervised exercise program available to them, a self-directed structured walking program should be encouraged.

- b. **Cilostazol** is a type 3 phosphodiesterase inhibitor that suppresses platelet aggregation and acts as a direct arterial vasodilator. Cilostazol also beneficially increases HDL, decreases triglycerides, and inhibits vascular cell adhesion molecule-1 expression, thereby decreasing vascular smooth cell proliferation. Randomized controlled trials of patients with moderate to severe claudication have demonstrated 40% to 60% increases in maximal walking distances with 12 to 24 weeks of therapy with cilostazol 100 mg twice daily. A trial of cilostazol, 100 mg twice daily, is recommended in all patients with PAD and intermittent claudication to relieve symptoms and improve walking distance (class I). Cilostazol is contraindicated in patients with congestive heart failure, owing to an increased risk of sudden death associated with related phosphodiesterase inhibitors. Common side effects associated with cilostazol include diarrhea, palpitations, and headaches.
 - c. **Pentoxifylline.** Oral pentoxifylline, 400 mg three times daily, can be considered as a second-line alternative to cilostazol in patients with symptomatic claudication (class IIb). Pentoxifylline is a methylxanthine derivative that functions as a vasodilator and an antiplatelet agent, reduces blood viscosity, and improves deformability of erythrocytes and leukocytes to exert its effects. Trials have been divergent on the efficacy of pentoxifylline and is felt to result in only marginal improvements in maximal walking distance and symptoms.
4. **Revascularization.** Revascularization is indicated for “lifestyle-limiting” claudication (after failed medical therapy), rest pain, ischemic ulceration, or gangrene. It may be **performed surgically or percutaneously**.
- a. **Percutaneous therapy.** In carefully selected patients, catheter-based revascularization is an attractive alternative to conventional surgical management. Percutaneous revascularization has a class I indication for individuals with lifestyle-limiting claudication when there is a reasonable likelihood of procedural success and there has been an inadequate response to conservative therapy. Percutaneous revascularization is recommended according to the TransAtlantic Inter-Society Consensus II (TASC II) guidelines, which divide lesion anatomy according to location, distribution, length, and likelihood of procedural success. TASC type A lesions are those in which endovascular therapy is recommended, and type B lesions are those in which endovascular therapy is preferred in most cases. For instance, TASC type A disease in the aortoiliac system is defined as unilateral or bilateral disease in the common iliac or external iliac arteries of short length (< 3 cm). In the femoral popliteal region, a type A lesion is defined as a single stenosis ≤ 10 cm in length or a single occlusion ≤ 5 cm in length. Translesional pressure gradients (criteria: threshold peak systolic difference 5 to 10 mm Hg prevasodilation and 10 to 15 mm Hg postvasodilation) should be obtained for angiographic lesions that appear moderately stenotic (e.g., 50% to 75%) prior to intervention (class I). The treatment of choice for focal aortoiliac disease is angioplasty with or without stenting. This approach has a technical success rate of 90%, 2 year patency rate of 73% to 84%, a complication rate of < 10% (usually related to the arterial access site), and periprocedural mortality rate of < 1%. For femoropopliteal disease, patency rates with percutaneous therapies are lower than those in iliac disease; therefore, angioplasty is utilized to manage focal disease after failure of medical therapy. Direct stenting as a primary therapy is not recommended for femoral, popliteal, or tibial arteries; however, stenting may be effective as salvage therapy after suboptimal or failed balloon angioplasty (class I).
 - b. **Surgical.** Similarly, surgical revascularization also has a class I indication for individuals with lifestyle-limiting claudication when there is a reasonable likelihood of procedural success and there has been an inadequate response to conservative therapy. Surgery is used to bypass long segments of diffuse disease

(particularly involving the femoropopliteal segment) or when endovascular therapy fails. Various conduits, such as reversed or in situ saphenous vein grafts, Dacron grafts, and polytetrafluoroethylene grafts, can be used. For severe disease below the popliteal artery, both percutaneous and surgical revascularization approaches have marginal outcomes with regard to limb salvage. In patients younger than 50 years, the efficacy of surgical intervention for symptomatic claudication is not well established due to the aggressive nature of their atherosclerosis and limited graft durability (class IIb). Given the coincidence of coronary artery disease in these patients, a thorough preoperative assessment of cardiac risk should be performed prior to vascular surgery.

III. LOWER EXTREMITY ANEURYSMS. Aneurysms of the peripheral arteries, as in the aorta, are most commonly due to atherosclerotic disruption of the arterial media. Up to 70% of lower extremity aneurysms involve the popliteal arteries. The incidence of bilateral involvement in lower extremity aneurysm is high (45% to 68%). The majority of patients (62%) with popliteal aneurysms have been reported to have concomitant abdominal aortic aneurysms (AAAs), and this coprevalence increases to 85% in patients with femoral artery aneurysms. Accordingly, patients diagnosed with peripheral arterial aneurysms, especially femoral or popliteal, should be screened with ultrasound for AAA and for the presence of contralateral lower extremity disease (class I). The greatest concern with lower extremity aneurysms is thrombosis and thromboembolism. Lower extremity aneurysms infrequently rupture (7% to 12%), but up to 60% will have an ischemic complication; therefore, acute limb ischemia is the most common presenting symptom. As an aneurysm increases in size, it can compress adjacent venous and lymphatic structures causing lower extremity edema. Given the risk of thrombosis, it is recommended that popliteal aneurysms > 2.0 cm (class I) and femoral artery aneurysms > 3.0 cm be repaired. Unless symptomatic, aneurysms of smaller caliber should be followed by annual arterial duplex ultrasound examinations (class IIa).

IV. UPPER EXTREMITY ARTERIAL DISEASE. In addition to atherosclerosis, the most common cause of upper extremity PAD, other pathologic states can result in stenosis of the upper extremity arteries. These disorders include vasculitis (particularly Takayasu and giant cell arteritis), FMD, thoracic outlet syndrome, ionizing radiation, and repetitive injury. Associated clinical symptoms include arm and hand claudication, digital ulceration, and neurologic symptoms caused by vertebral–subclavian steal. The diagnostic modalities are similar to those in lower extremity arterial disease. The simple clinical maneuver of checking blood pressure measurements in both arms is an excellent screening test for significant upper extremity PAD. Risk factor modification and revascularization (for symptomatic patients) are the mainstays of therapy. Finally, a high index of suspicion for concurrent cardiovascular and cerebrovascular disease should be maintained.

V. RENAL ARTERY DISEASE

A. Clinical manifestations. Renal artery stenosis (RAS) is commonly associated with two clinical syndromes: hypertension and ischemic nephropathy. Clues to the presence of RAS include the following: **abrupt onset of hypertension** (before age 30 years, often due to FMD, or after age 55 years, often due to atherosclerotic disease); **previously well-controlled essential hypertension that becomes resistant to medical therapy** (three-drug regimen including a diuretic); **azotemia**, which is unexplained or induced by ACE inhibitor administration; and **recurrent flash pulmonary edema**, often with normal left ventricular function (due to renin-angiotensin-mediated volume overload and peripheral vasoconstriction). Physical examination in RAS may reveal hypertension, epigastric bruits, and evidence of atherosclerosis in other vascular beds (e.g., carotid or femoral bruits and diminished pedal pulses). Renal imaging can reveal an atrophic kidney or a size discrepancy between the two kidneys.

- B. Etiology and natural history.** The most common causes of RAS are atherosclerosis and FMD. Atherosclerosis accounts for 90% of RAS and usually involves the ostium and proximal third of the main renal artery. The prevalence of atherosclerotic RAS increases with age, particularly in patients with diabetes, aortoiliac disease, coronary artery disease, or hypertension. Studies have suggested that the prevalence of RAS in patients with PAD may be as high as 59%. It is the most common cause of secondary hypertension, may account for 1% to 5% of all cases of hypertension, and may be the cause of end-stage renal failure in up to 20% of new dialysis patients. RAS is an independent risk factor of mortality in patients with other vascular diseases. Moreover, end-stage renal disease due to RAS is associated with the highest mortality (median survival of 2.7 years) among all dialysis-dependent patients. FMD accounts for < 10% of cases of RAS, but should be suspected in younger patients without atherosclerotic risk factors who present with RAS. It more frequently affects the distal two-thirds of the main renal artery and its branches, and in the most common type of FMD, medial fibroplasia, there is a characteristic “string of beads” appearance on angiography. The cause of FMD is unknown. Rarer causes of RAS include vasculitis, neurofibromatosis, congenital bands, extrinsic compression, and ionizing radiation.

C. Diagnostic evaluation

- 1. Laboratory studies.** Blood urea nitrogen and serum creatinine are readily available and are often used in practice as screening tools. Although azotemia and increased serum creatinine are neither sensitive nor specific for RAS, they may be the first clue to the disease. Urinalysis in RAS usually reveals proteinuria and a bland sediment. Because of the advent of sensitive and specific noninvasive imaging modalities, plasma renin activity and selective renal vein renin measurements are not recommended as screening tests to diagnose RAS (class III).
- 2. Duplex ultrasonography (DUS).** Arterial duplex uses a combination of B-mode ultrasound imaging and Doppler frequency spectral analysis. Elevated peak systolic velocities, the renal-to-aortic ratio, and the presence of color and spectral turbulence are criteria used to determine the presence of significant RAS. In addition, DUS allows for calculation of the renal resistive index (renal parenchymal peak systolic velocity minus end-diastolic velocity divided by the peak systolic velocity), which is a potential marker of renal parenchymal disease. Some data suggest that patients with an elevated resistive index may not improve after revascularization. DUS is inexpensive, widely available, and highly sensitive and specific for RAS when compared with angiography (reported sensitivities between 84% and 98% and reported specificities between 62% and 99%). It is also highly useful for surveillance of renal arteries after stenting, as flow through a stent can be easily detected, in contrast to MRA, which is limited by metal artifact. DUS for RAS must be performed in experienced centers. The test may be limited by difficulty in obtaining measurements due to excess bowel gas or obesity. It also has lower sensitivity (64%) for identifying accessory renal arteries, narrowing of which could also lead to the signs of RAS.
- 3. Renal scintigraphy.** Radionuclide renal imaging is used to assess differential renal blood flow and has been used in conjunction with captopril renography to attempt to diagnose RAS. Captopril renography precipitates an ACE inhibitor-mediated fall in glomerular filtration to amplify differences in renal perfusion consistent with RAS. Due to a relative lack of sensitivity (74%) and specificity (59%) compared with catheter-based angiography, captopril renography is no longer recommended for the screening of RAS (class III).
- 4. Magnetic resonance angiography.** MRA now has a class I indication as a test for the diagnosis of RAS, with reported sensitivity and specificity from 90% to 100% and 76% to 94%, respectively, when compared with angiography. MRA is noninvasive and has the ability to generate 3D reconstructions. Its limitations include expense, limited availability, lack of resolution in the setting of high-grade

stenosis (often appearing as an occlusion or loss of signal), a tendency to overestimate lesion severity, and difficulty with post-stent imaging due to artifact. It is also less sensitive for the detection of FMD, given that the typical arterial beading may be subtle and resolution of MRA is still limited, particularly of the distal renal vasculature. In addition, in patients with advanced renal insufficiency or renal failure, gadolinium-containing contrast agents have been linked to nephrogenic systemic fibrosis in 2% to 3% of patients (see Chapter 51). This has complicated the use of contrast-enhanced MRI in patients with RAS and renal insufficiency.

5. **Computed tomographic angiography.** Like MRA, CTA has the capability of producing excellent 3D images of the renal arteries as well as the aorta and other visceral vessels. CTA has a sensitivity and specificity for detecting significant RAS ranging from 59% to 96% and 82% to 99%, respectively. Contrast administration (100 to 150 mL) and radiation dose remain limitations of CTA. Unlike MRA, CTA does not have significant imaging artifact with metal clips or stents and, therefore, can be used to detect in-stent restenosis.
 6. **Renal arteriography.** This is the gold standard for the diagnosis of RAS. It allows for excellent visualization of the main renal and accessory renal arteries and their branches. Arteriography allows for assessment of the degree of stenosis visually and adds the ability to obtain hemodynamic measurements (gradients) across the stenotic lesions. Disadvantages include the requirement for intraarterial access and nephrotoxic radiocontrast.
- D. Treatment.** Despite antihypertensive therapy, RAS tends to progress and may be associated with renal ischemia and loss of renal function (i.e., renal insufficiency). Atherosclerotic nephropathy is complex and not simply related to stenosis of the renal artery. Examination of renal histology in patients with atherosclerotic nephropathy reveals other potential mechanisms for loss of function, including small-vessel occlusion from atheroemboli, intrarenal arterial stenoses, and preexisting hypertensive nephrosclerosis. Importantly, as with other peripheral vascular disease processes, a high index of suspicion for concurrent cardiovascular and cerebrovascular disease should be maintained.
1. **Medical therapy.** Aggressive antihypertensive therapy using multiple agents remains the mainstay of RAS therapy and is often the control arm of randomized trials of interventional approaches to RAS. ACE inhibitors, angiotensin receptor blockers, diuretics, β -blockers, calcium channel blockers, and various other antihypertensives have been shown to be effective in treating hypertension associated with RAS. ACE inhibitors and angiotensin receptor blockers should not be used in patients with bilateral RAS or a solitary kidney with RAS. However, these agents can be highly effective in the management of hypertension in patients with unilateral RAS (class I). Patients with RAS should be treated to achieve blood pressure targets consistent with the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of Hypertension. Aggressive atherosclerotic disease risk factor modification should be part of a comprehensive treatment plan.
 2. **Percutaneous revascularization.** The principle behind revascularization is that early restoration of renal artery patency in patients with atherosclerotic RAS may improve hypertension management and minimize progressive renal dysfunction; however, there is a paucity of data from controlled clinical trials to show that revascularization for RAS improves hypertension or delays renal dysfunction. Two small randomized trials demonstrated that patients treated with percutaneous renal artery angioplasty had improved systolic blood pressure and/or blood pressure control (as measured by a reduction in the number or dose of antihypertensive agents used) compared with patients treated with antihypertensive therapy alone. Response to percutaneous intervention is better among patients with FMD than those with atherosclerotic RAS, a finding that may be expected given the pathology that is seen at multiple levels in renal vasculature with atherosclerotic RAS. Congestive

heart failure and chronic obstructive pulmonary disease have been shown to be independent predictors of increased mortality in patients undergoing renal artery stenting; however, baseline azotemia remains the strongest predictor of long-term mortality (70% 5-year mortality rate with serum creatinine > 2.5 mg/dL).

Revascularization for RAS has been shown to stabilize or improve renal function in patients with symptomatic RAS up to 1 year after intervention. In the ACC/AHA PAD guidelines, the only class I indication for percutaneous renal artery revascularization is hemodynamically significant RAS in patients with recurrent unexplained pulmonary edema or congestive heart failure. Other clinical scenarios in which percutaneous renal artery revascularization for hemodynamically significant RAS can be considered (class IIa) are uncontrolled/malignant hypertension, progressive chronic kidney disease with bilateral RAS, RAS in a solitary functioning kidney, or unstable angina with RAS. A hemodynamically significant lesion in RAS is defined as any lesion with > 70% stenosis or a lesion that has 50% to 70% stenosis with a translesional pressure gradient > 20 mm Hg or mean gradient > 10 mm Hg. In terms of revascularization technique, renal artery stent placement has a class I indication for ostial atherosclerotic RAS. Stenting is also recommended as bailout therapy following failed angioplasty in renal FMD, although angioplasty alone is generally successful in this disorder. Predictors of poor outcomes with RAS interventions include significant proteinuria (> 1 g/d), renal atrophy, parenchymal renal disease, and diffuse renal arterial disease.

3. **Surgical revascularization.** Vascular surgery approaches to RAS include surgical bypass (aortorenal, celiac-renal, or mesenteric-renal) and endarterectomy. Perioperative mortality rates range from 1% to 5%. The comparable procedural success with percutaneous approaches and fewer major complications have led to a decline in the number of vascular surgeries for RAS. In the setting of RAS and aortic disease (either aneurysmal or occlusive), surgical revascularization with renal artery bypass grafting is the preferred approach (class I). Surgical revascularization is also recommended for patients with significant atherosclerotic RAS and clinical indications for intervention with multiple renal arteries or early branching main renal artery (class I). In patients with FMD, surgical revascularization is recommended for RAS associated with macroaneurysms or complex disease involving segmental renal arteries (class I).
4. **Controversies.** Among existing revascularization procedures for peripheral vascular disorders, renal artery stenting is possibly the most widely applied and poorly tested. To date, there are no published randomized controlled trials demonstrating the superiority of renal artery stenting over optimal medical therapy (risk factor modification, aggressive antihypertensive therapy, lipid reduction therapy, and aspirin) for RAS. In addition, the ability of renal artery stenting to decrease mortality or progression to dialysis or to provide prolonged benefits in blood pressure control remains uncertain. The National Institutes of Health (NIH)-sponsored Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL) trial is the first large randomized controlled trial comparing medical therapy with medical therapy plus renal artery stenting for the treatment of patients with systolic hypertension and RAS, and its findings are awaited with interest.

ACKNOWLEDGMENTS: *The author thanks Dr. Frank J. Zidar and Dr. Thomas Helton for their contributions to earlier editions of this chapter.*

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HELPFUL WEB SITES

<http://www.acc.org/clinical/guidelines/pad/index.pdf>
www.tasc-2-pad.org/
<http://www.padcoalition.org/wp>
<http://www.aboutpad.org>
<http://www.coralclinicaltrial.org>
<http://www.vdf.org>

CHAPTER

28

Hemal Gada

Carotid Artery Disease

I. EPIDEMIOLOGY AND ETIOLOGY OF STROKE

- A. Annually, there are nearly 800,000 strokes in the United States and 15 million strokes worldwide. Stroke is the **third leading cause of death** in Western societies and the leading cause of long-term disability in the United States.
- B. Ischemic stroke accounts for approximately 85% of all strokes and can be classified into two broad categories.
 1. **Embolic:** May be arterial (e.g., aortic atheroma or large vessel atherosclerosis in the carotid, vertebral, or basilar arteries) or cardiac (e.g., left ventricular thrombus postmyocardial infarction [post-MI], atrial fibrillation, valvular disorders, and cardiac tumors) in origin and most often occurs suddenly, with deficits indicating focal loss of brain function.
 2. **Thrombotic:** May be caused by stenosis of smaller intracerebral arteries, a hypercoagulable state, or a systemic inflammatory condition causing vasculitis, with symptoms that may fluctuate in presence and intensity.

II. NORMAL CAROTID ANATOMY

- A. The aortic arch normally gives rise to the innominate artery (aka brachiocephalic artery), the left common carotid artery (CCA), and the left subclavian artery (Fig. 28.1). The innominate artery bifurcates into the right CCA and the right subclavian artery. The **left common carotid arises from the aortic arch in 70% of people and from the innominate artery in 20% (“bovine arch” variant).**

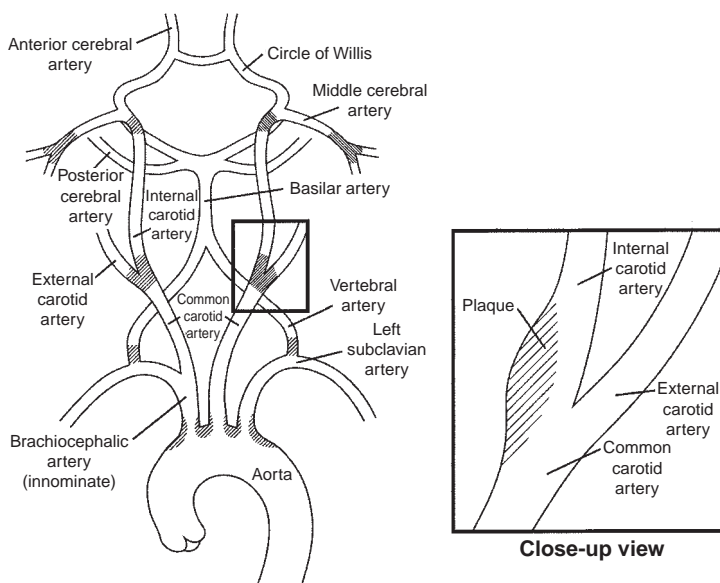


FIGURE 28.1 Normal anatomy of the aortic arch, great vessels, and circle of Willis. The shaded regions depict the areas most prone for the development of atherosclerosis.

- B. The aortic arch can be classified into three types based on the distance of the origin of the great vessels from the top of the arch (Fig. 28.2). The widest diameter of the left common carotid is used as a reference unit. If all the great vessels originate **within an arc of the aortic arch subtended by a line parallel to a horizontal reference line at the top of the arch and separated from the top reference line by the reference unit**, it is classified as a **type I arch**. In a **type II arch**, all the great vessels originate within an arc **within two reference units** from the top of the arch, and in a **type III arch** the great vessels **originate within an arc beyond two reference units** from the top of the arch. Type III arches are harder to access during percutaneous intervention than type I arches.
- C. The CCAs divide into the internal and external carotids at the C4-5 level in 50% of the patients. In approximately 40% of patients, the bifurcation is higher, and it is lower in the remaining 10%.
- D. The external carotid artery provides flow to the facial muscles, scalp, and thyroid. It has a complex system of collaterals, and symptoms from stenosis are rare.
- E. The circle of Willis provides collateral flow between the left and right hemispheres of the brain and connects the anterior and posterior circulation.

III. RISK FACTORS FOR CAROTID ATHEROSCLEROSIS

- A. **Smoking and age** are the two most important risk factors for developing carotid atherosclerosis. The others, in order of importance, are **hypertension, diabetes, gender (men more than women if younger than 75 years; women more than men if older than 75 years), and hyperlipidemia**. As with coronary artery disease (CAD), inflammation likely plays a major role in carotid disease. African American men and Hispanic Americans appear to have a higher incidence of carotid atherosclerosis. Some data suggest a role for chronic infection in the development of carotid disease.

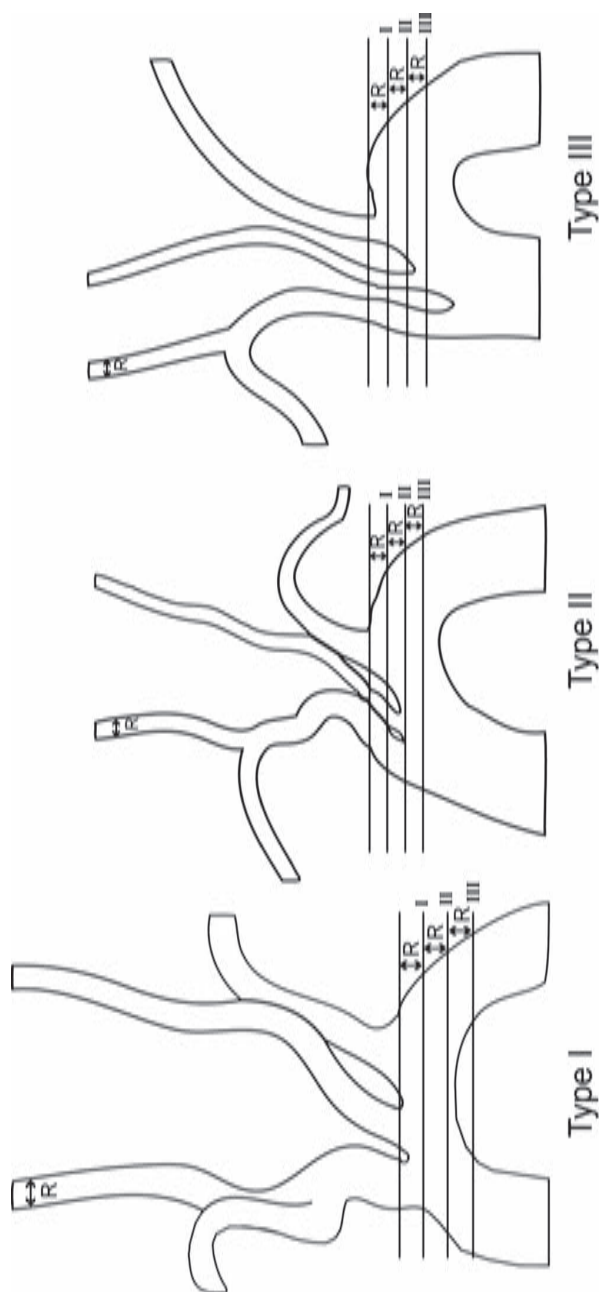


FIGURE 28.2 Aortic arch classification. The classification system is based on the distance of the origin of the great vessels from the top of the arch.

- B. Elevated serum lipoprotein(a) has been associated with intracranial, extracranial, and aortic large artery occlusive disease.
- C. Between 30% and 60% of patients with peripheral arterial disease have carotid disease, and approximately 50% to 60% of patients with carotid disease have severe CAD. However, only 10% of patients with CAD have severe carotid disease.

IV. PATHOPHYSIOLOGY

- A. As with coronary disease, atherosclerotic carotid disease usually develops at branch points and bends, especially at the bifurcation of the CCA and origin of the internal carotid artery (ICA) (Fig. 28.1).
- B. Plaque is most often localized at the carotid bifurcation and tends to extend from the outer wall of the carotid bulb into the ICA origin (Fig. 28.1).
- C. The reasons that carotid stenoses become symptomatic are not completely understood, but there is a linear increase in the risk of stroke as the stenosis increases to > 70%. Two hypotheses explain how carotid disease can cause stroke.
 - 1. **Carotid plaque is highly vascularized.** Rupture of this vasculature or rupture of the plaque can result in plaque hemorrhage or ulceration, with subsequent *situ thrombus* formation. This can lead to complete vessel obstruction or distal atherothromboembolism. This mechanism accounts for most cerebrovascular events caused by carotid disease.
 - 2. Larger plaques can result in high-grade carotid stenosis or obstruction, with subsequent ischemic stroke due to a reduction in cerebral flow, in the setting of inadequate or absent collateral circulation.

V. DIAGNOSIS

A. History and physical examination

- 1. **Careful history can aid in the localization of neurologic symptoms.** Hemispheric symptoms include unilateral weakness, numbness, difficulty with speech, and visual field defects, whereas vertebrobasilar symptoms can include cerebellar disturbances such as ataxia or brain stem symptoms including syncope, dysphagia, dysarthria, or diplopia. Amaurosis fugax is transient, unilateral vision loss ipsilateral to a carotid lesion.
- 2. **An assessment for the presence of a cervical bruit is an important part of the physical examination but should not be relied on as the sole marker for the presence of carotid disease.** In the North American Symptomatic Carotid Endarterectomy Trial (NASCET), the presence of a cervical bruit had an approximately 60% sensitivity and specificity for high-grade carotid stenosis. In the Framingham study, the presence of a carotid bruit in asymptomatic patients doubled the risk of stroke, but most of these strokes occurred in vascular beds different from those of the carotid bruit. The presence of a bruit may be a general marker for patients at higher risk for cerebrovascular and cardiovascular events.
- 3. **In addition to auscultation for carotid bruits, a complete evaluation in a patient with symptoms includes a focused neurologic examination to correlate symptoms with neurologic territory, a funduscopic examination to detect retinal embolization, and a cardiac examination to rule out potential cardioembolic sources for symptoms.**
- 4. All patients should have an evaluation of the carotid arteries after a stroke or a transient ischemic attack (TIA). The risk of a second stroke is elevated for several years after the first stroke or TIA. Symptomatic patients with 70% or more stenosis have an 8% risk of stroke at 30 days and a 13% annual incidence of stroke. The risk of stroke in asymptomatic patients increases as the degree of carotid stenosis increases. Asymptomatic patients with 60% or more stenosis have a stroke risk of approximately 2% per year. Asymptomatic patients with 80% or more stenosis have a risk of approximately 5% per year.

B. Duplex ultrasound

1. Although carotid angiography is the gold standard, duplex ultrasound is the most widely used method for the detection and quantification of carotid artery disease. It has a sensitivity and specificity of > 80% among patients with 70% to 99% stenoses and sensitivity and specificity of > 95% among patients with complete carotid occlusion. Due to its high sensitivity and specificity in severe carotid disease and its noninvasive nature, duplex ultrasound should be the first study performed to assess for carotid disease.
2. The ultrasound diagnosis of carotid stenosis is based largely on peak systolic and end-diastolic velocities in the ICA. Duplex ultrasound criteria for carotid stenosis vary by institution, and each vascular laboratory must assess the accuracy of its criteria for stenosis in a quality assurance program. Compared with angiography, duplex ultrasound is noninvasive, less expensive, and can be done at the bedside. Limitations include the inability to image intracranial disease, limited ability to assess collateral flow, occasional inaccuracy in distinguishing high-grade stenoses ("string sign") from complete obstructions, and the need for an experienced sonographer. Conditions that may elevate intravascular flow velocities, such as common carotid disease, vessel tortuosity, contralateral carotid disease, or presence of a carotid stent, may result in an artificially high estimate of ICA stenosis. The ability of ultrasound to assess the posterior carotid circulation is limited.

C. Computed tomography angiography (CTA)

1. CTA offers high sensitivity and specificity for the identification of severe (> 70%) carotid artery disease (sensitivity 75% to 100%, specificity 63% to 95%, negative predictive value up to 100%). CTA allows for visualization of the carotid artery lumen as well as adjacent bony and soft tissue structures. Advantages include high sensitivity (particularly for carotid artery occlusion), reproducibility, and the ability to visualize the entire carotid artery including the extracranial and intracranial portions. Disadvantages include cost and the need for contrast injection, which may be unsuitable for patients with chronic kidney disease or volume overload.

D. Magnetic resonance angiography

1. Contrast-enhanced magnetic resonance angiography (CEMRA) is rapidly gaining acceptance as a sensitive (91% to 95%) and specific (88% to 92%) test for severe carotid disease. Advantages include high sensitivity, reproducibility, and the ability to visualize the entire carotid artery including the extracranial and intracranial portions. The use of a paramagnetic agent as a vascular contrast confers higher quality images less prone to artifact. Disadvantages include high cost and the inability to study critically ill patients, claustrophobic patients, or patients with ferromagnetic implants such as pacemakers.
2. The combination of CEMRA and Doppler ultrasound results in a lower number of misclassifications and higher sensitivity and specificity for the diagnosis of severe ICA stenosis. When there is concern regarding the accuracy of one study, it is justifiable to perform both.

E. Contrast angiography

1. Contrast angiography with digital subtraction angiography (DSA) is the gold standard for assessment of carotid atherosclerosis. It allows the simultaneous assessment of the aortic arch, subclavian arteries, vertebral arteries, and intracranial circulation. Angiography enables the accurate assessment of collateral circulation. This is important because the presence of collateral circulation in medically treated patients with high-grade stenosis reduces the risk of ipsilateral stroke.
2. The risk of neurologic events during carotid angiography has historically been cited from as low as 0.5% for major events to as high as 4% for all events. In the hands of an experienced interventional cardiologist, the risk of stroke in one study was found to be approximately 0.5%. In our institution, 1 stroke was

observed in 580 consecutive diagnostic carotid catheterizations. Nonetheless, the risk–benefit ratio of performing carotid angiography must be carefully evaluated for each patient.

3. Two criteria are used to quantify carotid stenosis angiographically: the NASCET criteria and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria (Fig. 28.3). According to the NASCET criteria, the normal reference internal carotid diameter is the maximum diameter of the ICA distal to the lesion and distal to the carotid bulb. According to the ECST criteria, however, the normal reference diameter is determined by the estimated position of the external wall of the carotid bulb. The same lesion has a higher percentage of stenosis using the NASCET criteria compared with the ECST criteria. In addition, the NASCET criteria are difficult to apply in subtotal occlusions with collapse of the distal ICA due to underfilling. However, the NASCET criteria inherently have less variability and are now recommended as the standard for reporting of angiographic carotid stenosis in Medicare physician quality initiatives.

4. Technique

- a. Complete cerebral angiography involves angiography of the aortic arch and carotid arteries, intracerebral angiography, and angiography of the vertebral arteries and posterior circulation.
- b. A low-osmolar or iso-osmolar, nonionic, heparinized contrast agent should be used. In the absence of contraindications, the patient should be anticoagulated with 50 U/kg of intravenous heparin. The patient's head is often put in a holder or immobilizer to prevent inadvertent movement, and the patient is advised to look at the ceiling or keep his or her eyes closed. DSA should be used, if available, to improve resolution and minimize the amount of contrast needed. Before obtaining each cine angiogram, the patient should be instructed not to move, breathe, or swallow during image acquisition.
- c. Aortic arch angiography is performed using an angled pigtail catheter. Using a 0.035" guidewire, the pigtail catheter is positioned in the mid-portion of the ascending aorta, and a cine angiogram of the aortic arch is obtained in a left anterior oblique projection (approximately 45°).
- d. Carotid angiography can be safely performed using a Judkins right (JR4) or a Headhunter catheter. Alternatively, a Vitek catheter can be used with

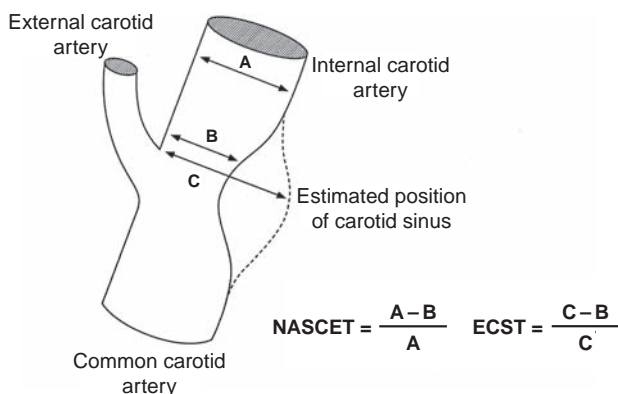


FIGURE 28.3 The North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trialists' (ECST) Collaborative Group criteria for determining the degree of carotid stenosis.

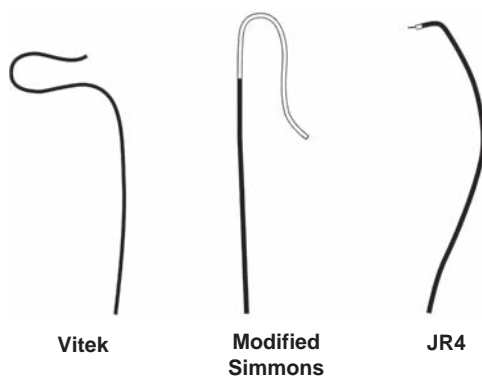


FIGURE 28.4 The three most common types of catheters used for carotid angiography.

bovine anatomy or type II or III arch. The Simmons catheter is useful in cases of severe tortuosity but requires reshaping in the aortic arch, which can lead to higher complication rates (Fig. 28.4). In the left anterior oblique projection, the JR4 catheter is positioned in the superior portion of the ascending aorta and rotated counterclockwise until it is positioned in the innominate artery. Nonselective cine angiography of the innominate, right subclavian, right carotid, and right vertebral arteries can then be performed with the image train in the right anterior oblique projection. In the right anterior oblique projection, a 0.035" wire (e.g., Stiff-Angled Glide, Magic Torque, and Wholey) is used to advance the JR4 catheter to selectively engage the right common carotid. Two basic views should be obtained for each carotid: an ipsilateral oblique view (30° to 45°) and a cross-table lateral view. The table should be positioned so that the carotid bifurcation is in the middle of the screen, and shutters and filters should be used to optimize image quality.

- e. For cerebral angiography, the patient's head is positioned in the center of the screen. Cine angiography is performed in the posteroanterior and lateral projections. It is important to continue the cine until the venous runoff has been captured to assess for intracranial arterial venous malformations and anomalous venous drainage. To selectively engage the left carotid, the catheter is positioned in the innominate artery so that the tip is pointing superiorly. The catheter is slowly pulled back, ensuring that the tip remains pointed superiorly, until the catheter tip exits the innominate and engages the left common carotid. The same views can then be obtained for the left carotid.

VI. MANAGEMENT OF CAROTID DISEASE

A. Medical management

1. **Risk factor modification.** Aggressive cardiovascular risk factor modification is recommended to reduce the risk of stroke and prevent the progression of existing disease, regardless of whether or not revascularization is indicated. Smoking cessation, blood pressure control to levels recommended by the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) guidelines (< 140/90 mm Hg and more aggressive control in patients with atherosclerotic cardiovascular disease,

chronic kidney disease, or diabetes), control of diabetes (HbA1c < 7%), and lipid management (goal low-density lipoprotein [LDL] < 100 mg/dL, < 70 mg/dL if high CAD risk) are important treatment goals for which to strive in any patient with carotid disease.

2. Antiplatelet therapy

- a. The Antiplatelet Trialists' meta-analysis including 73,247 high-risk patients found that antiplatelet therapy as secondary prevention resulted in a 27% (25% attributed to aspirin) relative reduction in the combined end point of vascular death, MI, and stroke.
- b. **Aspirin** is the most extensively studied antiplatelet drug for the prevention of stroke and other cardiovascular events and should be initiated in all patients with evidence of carotid atherosclerosis. Men whose 10-year risk for the development of stroke or MI is $\geq 10\%$ or greater should be started on low-dose (75 to 160 mg/day) aspirin for primary prevention. Women ≥ 65 years or older should be started on aspirin therapy (75 to 325 mg/day) for the primary prevention of MI and stroke. Aspirin therapy is also recommended in women younger than 65 years for the prevention of stroke when the benefits of ischemic stroke prevention outweigh the adverse effects of aspirin therapy.
- c. The **Clopidogrel** versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) trial demonstrated a decrease in the combined end point of vascular death, stroke, and MI with clopidogrel therapy compared with aspirin (5.32% vs. 5.83%) among patients with a history of stroke, MI, or symptomatic peripheral vascular disease. These data represented an 8.7% relative risk reduction ($p = 0.043$). Currently, there is no consensus on the use of clopidogrel for the primary prevention of stroke. Clopidogrel may be an option for the primary prevention of stroke in patients with moderate carotid stenosis who cannot tolerate aspirin.
- d. The Management of Atherothrombosis with Clopidogrel in High-Risk Patients with Recent Transient Ischemic Attacks or Ischemic Stroke (MATCH) study, which evaluated dual antiplatelet therapy with aspirin and clopidogrel versus clopidogrel alone in stroke patients with concomitant cardiovascular disease, patients who suffered a stroke while on a single antiplatelet agent, and patients with severe aortic arch disease, demonstrated an insignificant trend toward improved efficacy with dual antiplatelet therapy; however, there was a highly significant increase in life-threatening bleeding events.
- e. In contrast to MATCH, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial evaluated aspirin plus clopidogrel versus aspirin alone in patients with symptomatic cardiovascular disease or a constellation of cardiovascular risk factors. In this patient population, the combination of aspirin and clopidogrel was not more effective than aspirin alone in reducing the rate of MI, stroke, or death from cardiovascular causes. Dual antiplatelet therapy did improve rates of all-cause stroke (2.4% vs. 1.9%, $p = 0.05$), and subgroup analyses showed a significant 12.5% relative reduction in the risk of primary events in patients with established cardiovascular disease. As with all subgroup analyses, however, these results should be interpreted with caution.
- f. Low-dose aspirin (25 mg twice daily) plus dipyridamole (200 mg twice daily) has been found to be more beneficial than aspirin alone or dipyridamole alone for the secondary prevention of stroke in the European Stroke Prevention Study 2 (ESPS 2). Similarly, in the European/Australian Stroke Prevention in Reversible Ischemia Trial (ESPRIT), extended-release dipyridamole administered with aspirin was superior to aspirin alone in the prevention of MI, stroke, or vascular death.

- b. The JNC7 guidelines recommend that all patients with prehypertension (systolic blood pressure 120 to 139 mm Hg or diastolic blood pressure 80 to 89 mm Hg) undergo lifestyle modifications to lower blood pressure. Furthermore, all patients with blood pressure > 140/90 mm Hg (or > 130/80 mm Hg with diabetes or chronic kidney disease) should receive antihypertensive drug therapy to achieve their blood pressure goal. ACE inhibitors and diuretic agents remain first-line therapy in patients with cerebrovascular disease.

5. Anticoagulation

- a. There are no data specifically addressing the use of warfarin for primary stroke prevention in patients with documented carotid stenosis. However, one study has suggested that **low-dose warfarin may attenuate carotid plaque progression** in men. The use of warfarin for the secondary prevention of noncardioembolic strokes (including patients with carotid stenosis) is controversial. There was no clear benefit for low- and medium-dose oral warfarin therapy (international normalized ratio [INR] 2.0 to 3.0) for the secondary prevention of noncardioembolic stroke in the Warfarin–Aspirin Symptomatic Intracranial Disease (WASID) trial and a significant increase in adverse effects, including death, major hemorrhage, and MI, with warfarin use. High-dose warfarin (INR 3.0 to 4.5) for the secondary prevention of noncardioembolic stroke results in a high rate of bleeding complications, including hemorrhagic stroke, and should not be used.

B. Surgical management: carotid endarterectomy (CEA)

CEA is the standard of care for the reduction of stroke or TIA in patients with high-grade symptomatic or asymptomatic carotid stenosis. Several trials have firmly established the utility of CEA in preventing stroke in the presence of severe carotid stenosis as compared with medical therapy. It is important to keep in mind that high-risk patients were not enrolled in these trials. Because the risk of surgery among such patients probably would be higher than reported in these trials, extrapolation of these data to high-risk patients must be done with caution.

1. Major trials

a. Asymptomatic, low-risk patients

(1) Asymptomatic Carotid Atherosclerosis Study (ACAS)

- (a) A total of 1,662 patients with asymptomatic carotid stenosis of 60% or more were randomized to CEA or medical therapy. All patients were treated with aspirin (325 mg daily).
- (b) At a median of 2.7 years of follow-up, the estimated 5-year risk of stroke or death was 5.1% in the surgical arm and 11% in the medically treated arm ($p = 0.004$). The annual risk of stroke among patients in the medical arm was 2.3%. The perioperative stroke or death rate was 2.3%.

(2) Veterans Affairs Asymptomatic Carotid Stenosis Study

- (a) In this study, 444 men with 50% or more carotid stenosis were randomized to CEA or to medical therapy with aspirin.
- (b) The incidence of ipsilateral stroke was 4.7% in the surgical group versus 9.4% in the medical group, but there were no significant differences between the surgical and medical groups for all strokes and deaths (surgical 41.2% vs. medical 44.2%; RR 0.92, 95% CI 0.68 to 1.22).

(3) Asymptomatic Carotid Surgery Trial

- (a) In this trial, 3,120 patients with > 60% carotid stenosis were randomized to immediate CEA plus medical treatment versus medical treatment and deferred CEA.
- (b) The risk of perioperative stroke or death within 30 days of CEA was 3.1%. The estimated 5-year risks of stroke were 6.4% versus 11.8%, $p < 0.001$, for immediate CEA versus deferred CEA.

b. Symptomatic, low-risk patients

(1) The NASCET randomized 2,926 patients with symptomatic carotid stenosis (30% to 99%) to either medical therapy or medical therapy plus CEA. Recruitment of patients with severe carotid stenosis (70% to 99%) was stopped after 659 patients due to highly beneficial effect of CEA.

(a) A total of 659 patients with severe carotid stenosis (70% to 99%), ipsilateral hemispheric or retinal TIA, amaurosis fugax, or nondisabling stroke within 120 days were randomized to CEA or medical therapy.

(b) For those with severe (70% to 99%) carotid stenosis, the 30-day risk of stroke or death was 3.3% in the medical group and 5.8% in the surgical group. Two-year risk of any stroke was 26% in the medical group and 9% in the surgical group ($p < 0.001$), and the risk of major stroke or death was 18.1% in the medical group and 8% in the surgical group ($p < 0.001$). Patients with the most severe stenoses had the most benefit.

(c) A total of 2,267 patients with 30% to 69% stenosis, ipsilateral hemispheric or retinal TIA, or nondisabling stroke within 120 days were randomized to CEA or medical therapy. Patients with 50% to 69% stenosis had a 5-year stroke rate of 22.2% in the medical group and 15.7% in the surgical group ($p = 0.045$). Patients with 30% to 49% stenosis had a 5-year stroke rate of 18.7% in the medical group and 14.9% in the surgical group ($p = 0.16$).

(2) Veterans Affairs Cooperative Study

(a) In the Veterans Affairs Cooperative Study, 189 men with $> 50\%$ internal carotid stenosis with ipsilateral symptoms were randomized within 120 days of a neurologic event to CEA or medical therapy.

(b) At a mean of 11.9 months' follow-up, the incidence of stroke or TIA was 19.4% in the medical arm and 7.7% in the surgical arm ($p = 0.011$). The 30-day stroke or death rate was 6.6% in the surgical group and 2.2% in the medical group.

(3) The ECST Collaborative Group

(a) A total of 2,518 patients with symptomatic carotid stenosis were randomized to CEA or medical therapy. Patients ($n = 374$) with mild stenosis (0% to 29%) had low rates of ipsilateral stroke overall, and 3-year benefits of surgery were small and outweighed by operative risk. The ipsilateral stroke rate at 3 years of follow-up for patients with stenoses between 70% and 99% ($n = 778$) was 16.8% in the medical arm and 10.3% in the surgical arm.

2. Complications and management of patients after CEA

a. Major complications of CEA include MI, stroke, and death. Other complications include bleeding and wound hematoma, cranial nerve injury, wound infection, bradycardia, hyper- or hypotension, and, rarely, seizures and intracerebral hemorrhage.

b. After CEA and in the absence of contraindications, all patients should be treated with antiplatelet therapy.

3. The ASA/American College of Cardiology Foundation (ACCF)/AHA recommendations for CEA

a. Patients at average or low surgical risk who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax, within 6 months (symptomatic patients) should undergo CEA if the diameter of the lumen of the ipsilateral ICA is reduced $> 70\%$ as documented by noninvasive imaging or $> 50\%$ as documented by catheter angiography and the anticipated rate of perioperative stroke or mortality is $< 6\%$.

- b. Selection of asymptomatic patients for carotid revascularization should be guided by an assessment of comorbid conditions, life expectancy, and other individual factors and should include a thorough discussion of the risks and benefits of the procedure, with an understanding of patient preferences. It is reasonable to perform CEA in asymptomatic patients who have > 70% stenosis of the ICA if the risk of perioperative stroke, MI, and death is low.
 - c. Except in extraordinary circumstances, carotid revascularization is not recommended when atherosclerosis narrows the lumen by < 50%.
 - 4. **Combined CEA and coronary artery bypass grafting (CABG)**
 - a. Patients with severe coronary disease may have severe carotid disease, and surgery in this population is a high-risk procedure. The optimal treatment strategy remains unclear.
 - b. Options include simultaneous CEA and CABG, staged CEA followed by CABG, or staged CABG followed by CEA. In staged procedures, CEA first increases risk of perioperative MI, and CABG first increases risk of perioperative stroke.
 - c. Some investigators have reported better results with simultaneous procedures, but patient selection is likely an important factor in achieving satisfactory outcomes. A meta-analysis of 16 studies with a total of 844 combined procedure and 920 staged procedure patients reported a higher risk of death, stroke, or MI among patients undergoing combined compared with staged procedures. Percutaneous intervention may be a better choice for this patient population, and this is an area that requires further investigation.
- C. Percutaneous carotid intervention**
- 1. Since the first description of carotid angioplasty in 1980, a number of registry studies and trials have been published reporting high rates of procedural success. However, percutaneous carotid angioplasty is rarely performed as a stand-alone procedure because of unacceptably high rates of recoil, restenosis, and adverse procedural outcomes due to distal embolization. Carotid stenting has become the standard of care for patients undergoing percutaneous carotid intervention.
 - 2. Compared with angioplasty alone, carotid stenting improves procedural success rates, decreases periprocedural complications (including carotid artery dissection), and decreases restenosis. Several types of embolic protection devices are in use to prevent embolic complications of angioplasty and stenting. Results of observational studies have shown that embolic protection devices can reduce rates of adverse events during carotid artery stenting in experienced hands; however, inexperience can also worsen clinical outcomes when these devices are used. Benefit of these devices to prevent periprocedural events has not been established in randomized controlled trials.
 - 3. Several manufacturers have stents approved for use in the carotid artery. Balloon-expandable stents are generally not used for carotid stenting because of the potential for structural deformation that can occur as a result of external forces such as those caused by neck movement. Self-expanding stents, such as the Wallstent (Boston Scientific Corp, Quincy, MA), Acculink carotid stent (Abbott Vascular Devices, Redwood City, CA, formerly Guidant Corp), Xact carotid stent (Abbott Vascular Devices, Redwood City, CA), and the carotid SMART stent (Cordis Endovascular, Warren, NJ), are commonly used, as they continue to exert outward radial force after deployment and resist crushing.
 - 4. **Trials**
 - a. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) compared carotid angioplasty (without stenting) with CEA among patients with > 50% carotid stenosis and found similar rates of procedural bleeding, major stroke, or death between the two treatment strategies

at 30 days and 1 year. However, the CEA cohort did have a higher number of patients whose surgery was complicated by cranial nerve injury.

- b. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial was the first multicenter, randomized, controlled trial comparing carotid stenting with CEA in high-risk patients. Using the PRECISE nitinol stent (Cordis, Warren, NJ) and the AngioGuard (Cordis, Warren, NJ) distal protection device, 334 patients were randomized (167 to carotid stenting and 167 to CEA). An additional 409 patients were enrolled in a stent registry. The combined end point of death, stroke, and MI at 1 year was reached in 12.2% of patients in the stenting arm and 20.1% of patients in the CEA arm ($p = 0.004$ for noninferiority and $p = 0.053$ for superiority). This is the first randomized trial to show noninferiority of carotid stenting compared with CEA.
- c. The Carotid Revascularization Using Endarterectomy or Stenting Systems (CARESS) trial was a phase I multicenter, prospective randomized trial comparing carotid stenting with CEA in a broad-risk group of symptomatic (with > 50% stenosis) and asymptomatic patients (with > 75% stenosis). The combined primary end point of stroke and death was 3.6% for CEA and 2.1% for carotid stenting at 30 days, and 13.6% for CEA and 10.0% for carotid stenting at 1 year. The authors concluded that carotid stenting was equivalent to CEA in both symptomatic and asymptomatic patients at 1 year.
- d. The Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE) trial was a multinational, multicenter randomized trial evaluating carotid stenting with optional distal embolic protection versus CEA in 1,200 patients with symptomatic carotid artery stenosis. Unlike the SAPPHIRE trial, the SPACE trial was not limited to high-risk surgical patients. The SPACE trial was unable to demonstrate noninferiority of carotid stenting compared with CEA, as the rate of death or ipsilateral ischemic stroke at 30 days from procedure was 6.84% with carotid stenting versus 6.34% with CEA ($p = 0.09$). A criticism of the SPACE trial was that embolic protection devices were not required and were only utilized in 27% of the cases. However, no significant difference in the primary end point was observed with or without the use of embolic protection devices.
- e. The Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial was a multicenter, randomized, noninferiority trial comparing carotid stenting with CEA in symptomatic patients with 60% to 99% carotid stenosis. The EVA-3S trial enrolled moderate-risk surgical patients. EVA-3S was stopped prematurely after enrollment of 527 patients, due to higher rates of stroke and death at 1 month (9.6% vs. 3.9%, $p = 0.01$) and 6 months (11.7% vs. 6.1%, $p = 0.02$) with carotid stenting versus CEA. A criticism of the EVA-3S trial was the lack of experience of the operators taking part in the study, as the interventionalists were required to have completed only two procedures with any device prior to its use in the trial. Furthermore, the use of embolic protection devices was optional at the onset of the trial, and a significant difference in the 30-day outcome of stroke and death was present between patients treated with and without embolic protection devices (7.9% vs. 25%, respectively). The use of embolic protection devices during carotid artery stenting did not significantly improve rates of stroke or death versus CEA.
- f. The Carotid Revascularization Endarterectomy versus Stenting Trial (CREST) randomly assigned 2,502 patients with carotid atherosclerotic disease (47% asymptomatic, 53% symptomatic) to CEA or stenting. The primary end point of the trial, a composite of any stroke, MI, or death within

30 days following treatment plus any ipsilateral stroke during long-term follow-up (median 2.5 years), was similar for stenting and CEA (7.2% vs. 6.8%, respectively; $p = 0.51$). For patients aged 70 years or older, the rates of the primary end point and adverse events increasingly favored surgery over stenting. A secondary analysis showed that for the subgroup of patients with symptomatic carotid disease, the periprocedural rate of stroke and death was significantly higher for those assigned to stenting compared with CEA (6% vs. 3.2%, respectively; $p = 0.02$). However, for both stenting and CEA, the rates of stroke and death were at or below those of previous randomized controlled trials and were within the complication thresholds suggested in current guidelines for symptomatic and asymptomatic patients.

- g. In the International Carotid Stenting Study (ICSS, also known as CAVATAS 2), 1,713 patients with recently symptomatic carotid stenosis, suitable for either surgery or percutaneous intervention, were randomly assigned to treatment with either CEA or stenting. All patients had carotid artery stenosis of $> 50\%$ by NASCET criteria on noninvasive imaging. At 120 days, the proportion of patients who reached the combined end point of stroke, death, and MI was significantly higher for the stenting group than for the CEA group (8.5% vs. 5.2%, respectively; $p = 0.006$). Longer term follow-up of this patient group is currently pending.

5. Complications and management

- a. The major periprocedural complications during carotid stenting are stroke, MI, and death. Other complications include TIAs, access site bleeding, bradycardia, hypotension, seizures, and intracranial hemorrhage. **Advanced age and long or multiple stenoses have been found to be independent predictors of periprocedural stroke.** In one study, stenting in the presence of a contralateral occlusion, stenting after a previous CEA, or combined carotid and coronary interventions **did not** increase the risk of adverse outcomes.
- b. Periprocedural cerebrovascular events occur largely because of embolization of plaque debris and thrombus into the cerebral circulation during manipulation of the carotid plaque. Such emboli have been documented by the use of transcranial Doppler, and the amount of embolization has been correlated with the size of infarct during CEA. Emboli protection devices decrease the volume of distal embolization.
- c. Embolic protection devices fall into three general categories (Figs. 28.5 and 28.6): distal occlusion balloon protection, distal filter, and proximal occlusion balloon. The PercuSurge GuardWire (Medtronic, Minneapolis, MN) system provides occlusion of distal flow during carotid stenting, enabling the removal of embolized debris (Fig. 28.5). The AngioGuard (Cordis, Warren, NJ) is one example of a filtration umbrella mounted on a 0.014" guidewire, which is positioned distal to the plaque during stenting (Fig. 28.6). At the end of the procedure, the filter is removed using a retrieval catheter. Proximal occlusion balloon systems create reversal of flow in the ICA, preventing embolization of debris into the cerebral vasculature.
- d. **Bradycardia and hypotension** occur often during carotid stenting because of instrumentation and stretching of the carotid sinus baroreceptors. These hemodynamic effects are usually transient but can persist for up to 24 hours after intervention. **Symptomatic patients** should be managed with **intravenous crystalloid infusion and potentially a low-dose infusion of an inotropic agent (e.g., dopamine) or temporary pacing as required.** Unless the patient is hypertensive, antihypertensive and negative inotropic medications are usually withheld immediately preprocedure and postprocedure. Telemetry monitoring should be continued for 24 hours, and the nursing staff should perform frequent neurologic checks postprocedure. All patients

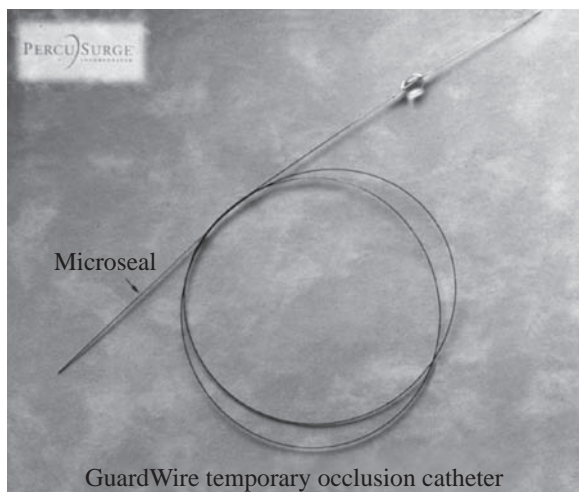


FIGURE 28.5 The PercuSurge GuardWire (Medtronic, Minneapolis, MN) system.



FIGURE 28.6 The AngioGuard (Cordis, Warren, NJ) emboli protection device.

should undergo a thorough and well-documented neurologic examination before and after the procedure. Standardized stroke scales are often utilized (e.g., NIHSS, Barthel, and modified Rankin).

- e. **Hyperperfusion syndrome**, manifested by strokelike symptoms and signs, can occur because of the rapid return of flow to a chronically underperfused cerebral vascular bed, with resultant disordered autoregulation. Risk factors include **severe hypertension, critical carotid stenosis, and contralateral carotid occlusion**. Cerebral hemorrhage is a dreaded complication of the hyperperfusion syndrome.

- f. Patients undergoing carotid stenting should be pretreated with aspirin (325 mg daily) and clopidogrel (75 mg twice daily) for 2 days before the procedure if possible. After the procedure, **lifelong aspirin therapy should be instituted**, and **clopidogrel (75 mg daily) should be continued for at least 6 weeks**. For patients with recurrent symptoms or a history of neck irradiation, clopidogrel should be continued indefinitely. The incidence of restenosis after carotid stenting is lower than after coronary stenting and ranges between 1% and 6% per year.
 - g. The routine use of adjunctive glycoprotein (GP) IIb/IIIa inhibitors has not been well studied in the setting of carotid stenting. Initial observational data suggest that their use may be safe. However, because of the potential for intracranial hemorrhage, especially among patients with hypertension or hyperperfusion syndrome after carotid stenting, and without clear evidence of benefit, GP IIb/IIIa inhibitors are not routinely used. Further studies are needed to better define the use of these agents in this arena; however, incremental benefit above and beyond the use of mechanical embolic protection devices may be difficult to demonstrate.
 - h. Patients with carotid stenosis frequently have concomitant CAD. Successful combined carotid stenting and percutaneous coronary intervention has been reported as a simultaneous procedure, and the two are frequently performed as staged procedures with satisfactory outcomes.
- 6. The ASA/ACCF/AHA recommendations for carotid stenting**
- a. Carotid stenting is an indicated alternative to CEA for symptomatic patients at average or low risk of complications associated with endovascular intervention when the diameter of the lumen of the ICA is reduced by > 70% by noninvasive imaging or > 50% by catheter angiography and the anticipated rate of periprocedural stroke or mortality is < 6%.
 - b. It is reasonable to choose carotid artery stenting over CEA when revascularization is indicated in patients with neck anatomy unfavorable for arterial surgery.
 - c. **Prophylactic carotid artery stenting might be considered in highly selected patients with asymptomatic carotid stenosis (minimum 60% by angiography and 70% by validated Doppler ultrasound), but its effectiveness compared with medical therapy alone in this situation is not well established.**

ACKNOWLEDGMENTS: *The author thanks Dr. Adnan Chhatriwalla and Dr. Christopher Bajzer for their contributions to earlier editions of this chapter.*

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SECTION

VI

Adult Congenital Heart Disease

EDITOR

Richard A. Krasuski

Atrial Septal Defect and Patent Foramen Ovale

I. INTRODUCTION

- A. Atrial septal defects (ASDs) constitute approximately 5% to 10% of congenital heart disease. Excluding bicuspid aortic valve and mitral valve prolapse, ASD is the most common form of congenital heart defect found among adults and is the most common acyanotic shunt lesion in adults as well.
- B. Often, an atrial communication may go unrecognized into adulthood because the clinical symptoms and physical manifestations can be subtle.
- C. Although survival into adulthood is the rule, the overall life expectancy is decreased in patients with an unrepaired ASD. Long-term exposure to chronic right heart volume overload can have deleterious effects, such as atrial arrhythmias, pulmonary vascular disease, and right heart failure. These clinical findings are directly related to patient age, with almost all patients becoming symptomatic by the fifth or sixth decade. The presence of an atrial communication is also a potential source of paradoxical embolus.
- D. A patent foramen ovale (PFO) is a specific form of interatrial communication caused by incomplete closure of the foramen ovale after birth. PFOs are present in 25% to 30% of the general population. The prevalence of PFO in patients with cryptogenic stroke is approximately 40% to 50%.
- E. Atrial septal aneurysms are congenital outpouchings of the atrial septum, near the fossa ovalis. These can perforate, resulting in an ASD with left-to-right shunting of blood. Atrial septal aneurysms can be detected in up to 10% of patients undergoing echocardiography and in up to 30% of patients with cryptogenic stroke, generally with a concomitant PFO.

- II. ANATOMY AND EMBRYOLOGY.** The primitive atrium is first partitioned into right and left atria by growth of the septum primum—a thin, crescent-shaped membrane that grows from the roof of the primitive atrium toward the endocardial cushions located between the atria and ventricles. An atrial communication initially persists as the foramen primum, composed of the free edge of the septum primum and the endocardial cushions. Before closure of the foramen primum, fenestrations develop in the septum primum that coalesce to form the ostium secundum. As the septum primum then fuses with the endocardial cushions, the ostium secundum maintains a right-to-left atrial flow that is important in the fetal circulation. **Failure of this fusion results in the development of a primum ASD.** A second septum, the septum secundum, then forms to the right of the septum primum, growing toward the endocardial cushions and usually closing the ostium secundum. **Failure to close the ostium secundum results in the formation of a secundum ASD.**

The septum secundum forms an incomplete partition of the atria, leaving a foramen ovale (i.e., fossa ovalis). The remaining septum primum tissue on the left atrial (LA) side

becomes a flap valve, or valve of the foramen ovale, and allows for the continued right-to-left shunting in the fetal circulation. At birth, when LA pressure increases, the septum primum flap closes and eventually fuses to anatomically seal the atrial septum. A “true ASD” results from a deficiency in septal development or from resorption of atrial tissue, whereas a **PFO results from failure of this septum primum flap to adequately seal the fossa ovalis**. At autopsy, a “probe-patent” PFO remains in 25% to 30% of patients.

During development, if there is overabundant or weakened septal tissue, the septum becomes very mobile. This can be visualized during echocardiography, and the degree of excursion can be measured. If the maximal excursion of the interatrial septum is **15 mm or more**, this abnormality is called an **atrial septal aneurysm**. If the amount of septal excursion is < 15 mm, it is referred to as a redundant atrial septum.

ATRIAL SEPTAL DEFECTS

I. ASD TYPES (Fig. 29.1)

- A. **Ostium secundum** defects or **secundum ASDs** constitute the most common type, accounting for 70% to 75% of ASDs. This defect, a true defect of the atrial septum, is located in the midportion of the atrial septum, within or including the fossa ovalis. Defects result from a deficient septum primum or an abnormally large foramen secundum. This type of ASD is two times more common in female patients. Isolated secundum ASD has been associated with mitral valve prolapse and other forms of congenital heart disease. It may also be associated with rheumatic mitral stenosis (i.e., Lutembacher syndrome).
- B. **Ostium primum** defects or **primum ASDs** account for 15% to 20% of ASDs and are part of the spectrum of atrioventricular (AV) septal defects (also known as AV canal defects or endocardial cushion defects). These defects occur in the inferior–anterior portion of the atrial septum and are frequently associated with a cleft in the anterior leaflet of the mitral valve, leading to varying degrees of mitral regurgitation. In their complete form, they include a large ventricular septal defect and a common

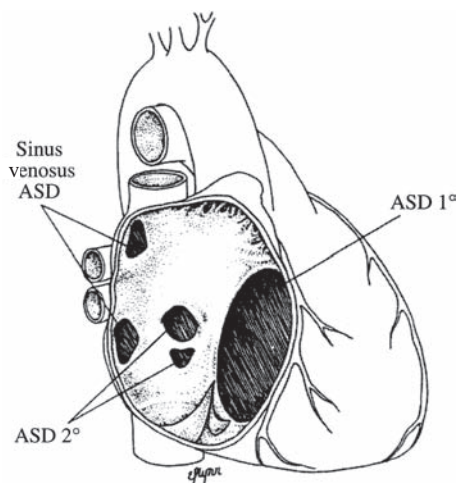


FIGURE 29.1 Diagrammatic representation of common atrial septal defects. ASD, atrial septal defect; 1°, primum; 2°, secundum. Reproduced from Fyler DC, ed. *Nadas Pediatric Cardiology*. Philadelphia, PA: Hanley & Belfus; 1992, with permission.

AV valve. Depending on the severity of dysfunction of the mitral valve, these patients may become symptomatic at a young age. This defect in the inlet septum is the most common ASD associated with Down's syndrome.

- C. **Sinoseptal** defects constitute the remaining 5% to 10% of septal defects. Distinct from the true ASDs described previously, these lesions involve the portion of the atrial wall derived from the sinus venosus (i.e., there is no direct communication between the right and left atria). **Sinus venosus defects** are typically at the orifice of the superior vena cava (SVC) at the junction of the right atrium or, less frequently, in the region of the inferior vena cava (IVC). These sinus venosus defects are frequently associated with partial anomalous pulmonary venous drainage of the right pulmonary veins and require a high index of suspicion for diagnosis because they are generally not visualized by standard transthoracic echocardiography (TTE). Transesophageal echocardiography (TEE) is generally required for visualization in adults. Magnetic resonance imaging (MRI) or computed tomography may also be used for diagnosis. These defects should be considered in any patient with unexplained right atrial (RA) or right ventricular (RV) dilation. An uncommon sinoseptal defect is the partially or completely **unroofed coronary sinus**, which is located inferior and slightly anterior to the fossa ovalis. These defects are commonly associated with other forms of congenital heart disease, such as complete AV septal defect, or can be associated with an absence of coronary sinus and a left SVC that drains into the left atrium.

- II. **PATHOPHYSIOLOGY.** The magnitude and direction of the shunt through the ASD depend on the size of the defect as well as the diastolic filling properties of the ventricles. Any condition that causes reduced left ventricular (LV) compliance, such as LV hypertrophy or LV scar, or increased LA pressure, such as mitral stenosis, will increase the degree of left-to-right shunting. Conversely, conditions that cause reduced RV compliance, such as pulmonary hypertension or pulmonary stenosis, or increased RA pressure, such as tricuspid stenosis, will reduce the degree of left-to-right shunting and, in some instances, even lead to shunt reversal. In general, the ASD must be at least 10 mm in its greatest dimension to cause a significant shunt, although this can be hard to measure, as most ASDs are not circular. A left-to-right shunt is considered significant when the ratio of pulmonary-to-systemic blood flow, or shunt fraction (Q_p/Q_s), is $> 1.5:1.0$ or when right heart chamber dilation is present.

- III. **CLINICAL MANIFESTATIONS.** The clinical presentation of a patient with an ASD results from the effects of long-term left-to-right shunting and subsequent volume loading of the right heart. The age at which the symptoms occur is variable and does not necessarily depend on the size of the defect.

- A. **Exercise intolerance** with **fatigue** and **dyspnea** may occur, but it is frequently not appreciated by the patient until after the defect has been closed. Late findings include **supraventricular arrhythmias**, such as atrial fibrillation or flutter, severe irreversible **pulmonary vascular disease**, and, eventually, **right heart failure**. Occasionally, a **paradoxical embolus** causing a stroke or transient ischemic attack (TIA) is the first clue to an ASD.
- B. The physical findings may include a hyperdynamic cardiac impulse, the characteristic **widely or fixed split second heart sound**, and a **soft systolic murmur at the second left intercostal space** due to increased flow across the pulmonary valve. If the shunt is more than a shunt fraction (Q_p/Q_s) of 2.5:1, there may be a diastolic murmur secondary to increased flow across the tricuspid valve. A loud P_2 component of the second heart sound indicates the presence of pulmonary hypertension, which can affect up to 20% of patients; if cyanosis is present, this generally suggests advanced pulmonary hypertension with reversal of shunt flow (**Eisenmenger syndrome**). An important clue to the presence of Eisenmenger syndrome is an oxygen saturation that does not significantly improve with supplemental oxygen.

Another physical examination finding that may be encountered is a holosystolic murmur characteristic of mitral regurgitation, which is often heard in a patient with a primum ASD.

IV. LABORATORY EXAMINATION

A. Electrocardiogram (ECG). The ECG can provide clues to the possibility of an ASD. The rhythm may be sinus, but may also be atrial fibrillation or atrial flutter. Inverted P waves in the inferior leads suggest an absent or nonfunctional sinus node, as may be seen with a sinus venosus defect.

1. Secundum ASD

- (a) RSR' pattern in lead V_1
- (b) QRS duration < 0.11 seconds (incomplete right bundle branch block)
- (c) Right-axis deviation
- (d) RV hypertrophy
- (e) First-degree AV block (20%)
- (f) RA enlargement (about 50%) with a prominent P wave in lead II

2. Primum ASD

- (a) RSR' pattern in lead V_1
- (b) Left-axis deviation
- (c) First-degree AV block, classically seen with right bundle branch block and left anterior fascicular block

B. Chest radiography may reveal cardiomegaly due to right heart enlargement. With large left-to-right shunts, the central pulmonary arteries and vascular markings may appear prominent. In the setting of advanced pulmonary vascular disease, however, the pulmonary arteries may appear large but have oligemic peripheral lung fields, so-called vascular pruning.

V. DIAGNOSTIC STUDIES

A. Echocardiography is the primary means by which an ASD is diagnosed. TTE can document the size of the defect as well as the direction of the shunt flow and occasionally the location of the pulmonary veins in the younger patient. In the adult, transesophageal studies are generally required for a full anatomic assessment. An ASD should be suspected when right-sided chamber enlargement is noted on echocardiography and no other cause is identified.

- 1. Typical transthoracic views for imaging an ASD include the parasternal short-axis view, the apical four-chamber view, and the subcostal coronal and sagittal views. Findings include RA and RV enlargement, which indicate a functionally important defect. An estimate of RV pressure should be made via the jet of tricuspid insufficiency, and evidence for RV pressure and volume overload should be noted via observation of septal motion in systole and diastole, respectively. Evidence of left-to-right (or right-to-left) shunting across the defect should be demonstrated using color Doppler techniques. Evidence of RA and RV enlargement in the absence of an obvious cause on echocardiography, such as tricuspid regurgitation or an ASD, should prompt a search for a sinus venosus defect and/or partial anomalous pulmonary venous drainage. Intravenous contrast (i.e., agitated saline) and TTE can identify a shunt, but TEE is usually required to demonstrate a sinus venosus defect. Of note, in isolated partial anomalous pulmonary venous return, the intravenous contrast study will be negative.
- 2. TEE is usually required in the adult patient for further anatomic definition and to determine whether the defect is amenable to percutaneous closure. Contrast studies with agitated saline are helpful in confirming the presence and location of atrial shunting. The midesophageal four-chamber and bicaval views are preferred, with injection of agitated saline through an upper extremity vein. Injection into the left arm may be particularly helpful to establish the presence of a

persistent left SVC that drains into the coronary sinus or directly into the left atrium. In the diagnosis of a sinus venosus defect, care must be taken to evaluate the location of the pulmonary veins for evidence of anomalous drainage.

B. Cardiac catheterization is typically not required for diagnostic purposes except to assess pulmonary pressures and resistance, to assess for coronary artery disease before planned surgical closure in the adult patient, or as part of a planned transcatheter device closure. Right heart catheterization can be performed in most cases using a standard end-hole catheter. The lateral camera is helpful in directing the catheter posterior before advancing across the ASD. Our standard is to perform a complete right heart catheterization, including oximetry measurements and hemodynamic assessment.

1. Oximetry samples obtained during catheterization demonstrate a step-up within the right atrium due to shunting across the defect. Careful interrogation of innominate vein saturation and SVC saturation is important to exclude a step-up at the SVC level that would support the existence of associated partial anomalous pulmonary venous drainage. Desaturation in the left atrium systemically confirms right-to-left shunting and should prompt further investigation of RV and pulmonary artery pressures. Other diagnoses producing a similar picture include large ventricular septal defects with tricuspid regurgitation, partial or complete AV canal defects, or systemic arteriovenous fistulas.

The significance of the defect can be assessed by calculating the **shunt fraction** (Q_p/Q_s), which is the ratio of pulmonary blood flow (Q_p) to systemic blood flow (Q_s). Oximetry values, obtained during right heart catheterization and used previously to determine if a step-up is present, can be helpful for shunt calculation as follows:

$$Q_p/Q_s = \frac{\text{aortic saturation} - \text{mixed venous saturation}}{\text{pulmonary vein saturation} - \text{pulmonary artery saturation}}$$

The mixed venous saturation is obtained in the setting of an ASD by multiplying the SVC saturation by 3, adding the IVC saturation, and then dividing the sum by 4. If the pulmonary vein saturation is not directly measured, it can be assumed in the absence of considerable lung disease to be 95%.

2. Hemodynamic assessment may reveal modest elevations in RV and pulmonary artery pressures. An important assessment is comparison of pulmonary artery pressure with systemic pressure and measurement of pulmonary vascular resistance. If pulmonary pressures are elevated, the response to oxygen or other vasodilators should be assessed. Alternatively, the ASD can be balloon occluded with assessment of hemodynamics to ensure that closure is safe. Examples of the usual catheterization findings with and without pulmonary vascular disease are illustrated in Figure 29.2.

Using a derivative of Ohm's law, $P = Q \times R$, an ASD will increase the flow (Q) to the lungs, and, therefore, increase the pulmonary pressure (P) without a significant change in resistance (R). Findings that may preclude eventual ASD closure include one or more of the following: pulmonary vascular resistance more than one-half of the systemic vascular resistance or an indexed pulmonary vascular resistance > 7 Wood units/m².

3. Angiography is typically not necessary for diagnostic purposes. Some transcatheter closure device protocols include angiography, typically performed in the right pulmonary vein or levophase from a main pulmonary artery injection in the left anterior oblique and cranial projections. This may be an important way to confirm the absence of additional defects, such as partial anomalous pulmonary venous drainage, before proceeding with transcatheter device closure.
- C. Cardiac MRI** can be helpful, as it can provide additional information beyond echocardiography. MRI provides an excellent assessment of RV size and function,

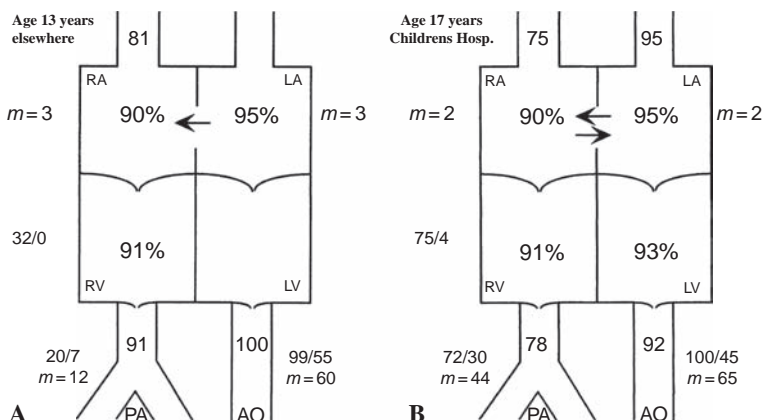


FIGURE 29.2 Catheterization data derived from two studies of the same female patient. The data obtained at age 13 (A) were interpreted as compatible with a small atrial septal defect of insufficient size to require closure. Some years later, she had developed pulmonary vascular obstructive disease (B) and was no longer shunting enough to recommend surgery. Death occurred 5 years later. AO, aorta; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle; numeric values within the schematic, oxygen saturation (%); numeric values outside the schematic, pressure (mm Hg). Adapted from Fyler DC, ed. *Nadas Pediatric Cardiology*. Philadelphia, PA: Hanley & Belfus; 1992.

especially if views obtained with echocardiography are not diagnostic. MRI is also excellent at determining the location of the pulmonary veins as well as calculating ventricular volumes and shunt fraction.

VI. TREATMENT. Medical intervention is typically not required preoperatively, because many patients are asymptomatic. Congestive symptoms may be improved with standard diuretic therapy. Rhythm disturbances such as atrial fibrillation require attention with respect to rate control and anticoagulation. Endocarditis antibiotic prophylaxis during dental procedures is not required in the setting of an isolated ASD before surgery, but it is warranted for 6 months after surgical or device closure (AHA/ACC class IIa).

A. Surgical or transcatheter therapy. The mainstay of therapy is closure of the defect by surgical or transcatheter techniques. Because of the reduced life expectancy associated with an unrepaired ASD, closure is recommended at diagnosis if there is evidence of a hemodynamically significant shunt ($Q_p/Q_s \geq 1.5:1$), evidence of right heart dilation, and evidence of probable paradoxical embolism or associated symptoms. In the setting of pulmonary hypertension, pulmonary reactivity to vasodilators should be documented and a net left-to-right shunt demonstrated during catheterization before consideration for closure. Alternatively, the defect can be temporarily balloon occluded at the time of catheterization, and the hemodynamic effects are directly measured. Situations in which ASD closure should not be pursued are listed in Table 29.1 and include advanced pulmonary hypertension (Eisenmenger syndrome) and severe LV dysfunction with elevated LA pressure.

B. Primary surgical closure has been the standard approach for many years. Generally, surgical closure is the treatment of choice for ostium primum and sinus venosus defects. Patients with secundum ASDs and anatomy that is not amenable to percutaneous closure (ASD diameter > 35 mm; inadequate septal rims to permit device deployment; or close proximity to AV valves, coronary sinus, or venae cavae) are

TABLE 29.1 **Conditions Where Atrial Septal Defect Closure Is Not Favored**

Defect is too small to be hemodynamically significant
Pulmonary hypertension is too advanced
Severe LV dysfunction, where ASD is acting as a “pop-off” valve for the left ventricle
In most cases where ASD is diagnosed in pregnancy, closure can be postponed until 6 months after delivery

ASD, atrial septal defect; LV, left ventricular.

also candidates for open surgical closure. Depending on the defect size and location, the secundum ASD can be closed by primary suture or, if needed, by the use of an autologous pericardial or synthetic patch. Ostium primum defects require patch closure as well as repair of the likely cleft mitral valve. Repair of sinus venosus defects is technically more challenging, as the pulmonary veins often have anomalous drainage and require rerouting.

1. Important preoperative risk factors include older age at operation, presence of atrial fibrillation, and elevated pulmonary pressure and resistance.
2. Postoperatively, patients are at risk for heart block, which is a significant complication in these cases. They are also at risk for postpericardiotomy syndrome, more so than after other surgery for congenital defects. Atrial arrhythmias may persist in short-term and long-term follow-ups because the RA and RV sizes may take time to return to normal, so anticoagulation is often recommended for several months after surgery. In some centers, prophylactic β -adrenergic blockade is advocated empirically for 3 to 6 months after surgery.

C. **Transcatheter closure** of a secundum ASD has become an attractive alternative to surgical closure and is now considered the treatment of choice. Any patient with an isolated secundum ASD may be suitable for transcatheter closure, which is generally assisted with TEE or intracardiac echocardiography in addition to fluoroscopy. Catheter closure decreases hospital length of stay, avoids surgical wounds and their possible complications, and significantly speeds up postprocedure recovery. With the devices available today, defects with a resting diameter of < 35 mm may be considered. In general, the gently stretched diameter of the defect is approximately 6 to 8 mm greater than the resting diameter. The defect must be located centrally with adequate room for the device to be positioned, without interference of other intracardiac structures such as the AV valves, coronary sinus, or pulmonary veins. The US Food and Drug Administration (FDA) has approved two devices for the closure of secundum ASDs: the Amplatzer Septal Occluder (AGA Medical Corporation, Golden Valley, MN) approved in December 2001 and the Helex Septal Occluder (WL Gore & Associates, Flagstaff, AZ) approved in August 2006. Studies have proved the safety and efficacy of catheter-based closure of a secundum ASD compared with surgical closure. The Amplatzer device consists of two disks made of Nitinol wire mesh filled with polyester fabric and separated by a narrower waist, which is appropriately fitted by balloon sizing. It is inserted percutaneously through a 6F to 12F sheath, depending on the device size required. The Helex device is also disklike and consists of expanded polytetrafluoroethylene (ePTFE) patch material supported by a single Nitinol wire frame. Major complications, such as cardiac perforation or device embolization, occur very rarely (generally fewer than 1% of cases), and successful closure of the defect is achieved in up to 95% of all patients. After closure, antiplatelet therapy, frequently aspirin and clopidogrel, is prescribed for a minimum of 6 months, after which time the device is generally believed to have endothelialized.

VII. PROGNOSIS. Hemodynamically significant ASDs are associated with increased morbidity and mortality. Long-term outcomes can be improved by closing these defects, especially if performed early in life. Atrial arrhythmias are common, especially in older patients, and are the result of long-standing atrial stretch. Arrhythmias, particularly atrial flutter and fibrillation, contribute to a significant portion of the morbidity and mortality of older patients, particularly the risk of systemic embolization and the resultant stroke. It has been demonstrated that age at the time of surgical repair is inversely related to the risk of subsequent atrial fibrillation or flutter after repair and argues for earlier closure. Some have advocated for consideration of a concomitant ablation procedure in high-risk patients, but the available data do not generally support this.

The functional capacity of patients frequently improves after closure of the ASD, and often they do not realize how severely their functional capacity had been affected until after the defect is closed. In addition, improvements in LV filling and systemic cardiac output are seen rapidly after defect closure. Reduced RA and RV volumes can be seen within 24 hours and continue to improve over the course of the first year following closure.

PFO AND ATRIAL SEPTAL ANEURYSM

I. PATHOPHYSIOLOGY. PFO can result in transient right-to-left shunting of blood flow, usually when RA pressure exceeds LA pressure such as during coughing or straining. These defects generally do not cause significant hemodynamic derangements. The clinical importance of an atrial septal aneurysm or a PFO is its impact on the risk of stroke. PFO features that increase the risk of a paradoxical embolus include large tunnel lengths (≥ 4 mm), high mobility of the valve of the foramen ovale, a well-formed eustachian valve, and a resting right-to-left shunt.

II. CLINICAL MANIFESTATIONS. Generally these defects are asymptomatic, most often coming to attention in patients with cryptogenic (unexplained) stroke. PFO is more common in patients with cryptogenic stroke than in the general population, but PFO alone has not been shown to be an independent risk factor for cryptogenic stroke. There are now accumulating data to suggest that an isolated PFO is not associated with an increased risk of recurrent ischemic stroke. The data in patients with both a PFO and an ASD are conflicting but suggest increased risk of recurrent stroke when both lesions are present. PFO should be suspected in young patients who sustain a stroke, as more than one-half of stroke patients younger than 45 years have a PFO. Other less common clinical associations with PFO include migraine headaches, platypnea-orthodoxia syndrome, and decompression illness in divers and those who work in high altitudes.

III. DIAGNOSTIC STUDIES. **Echocardiography** can easily differentiate between an ASD and a PFO if the interatrial septum is well visualized. If this is not possible via a transthoracic approach, a TEE may be necessary. A simple way to determine if a shunt is present is the “**bubble study**,” which is the injection of agitated saline via an upper extremity vein. If shunting is not present at rest, the patient can perform a Valsalva maneuver, which augments right-to-left shunt. If bubbles can be seen in the left atrium or the left ventricle within three cardiac cycles on TTE, the diagnosis of an interatrial right-to-left shunt is established. Generally, administration of agitated saline in patients with suspected right-to-left shunts is considered safe, but there have been rare case reports of cerebral ischemic events from passage of bubbles into the systemic circulation.

TEE will likely be required in most adults for better visualization of the interatrial septum. TEE helps to differentiate between a PFO and a secundum ASD, both of which can have positive bubble studies. TEE also allows assessment of other potential sources of emboli, such as atheroma in the aortic arch, thrombus in the LA appendage, or cardiac tumors.

TABLE 29.2 Contraindications to Percutaneous Patent Foramen Ovale Closure

Presence of an alternative source of emboli
Severe pulmonary hypertension
Recent gastrointestinal bleeding
Presence of congenital heart defect that needs surgical repair
Documented hypercoagulable state
Hypersensitivity or contraindication to antiplatelet or anticoagulant therapy
Unexplained fever or infection

IV. TREATMENT. Unfortunately, there is no clear consensus on primary or secondary prevention measures for patients found to have a PFO or atrial septal aneurysm. In general, atrial septal abnormalities are not treated for primary prevention of stroke. Regarding secondary prevention, most patients with neurologic events are treated with antiplatelet agents (either aspirin or a thienopyridine, or both), anticoagulants (warfarin), and percutaneous or surgical closure, although no clear consensus exists and the only randomized controlled study reporting results to date failed to demonstrate a benefit of closure over medical therapy. The CLOSURE I trial (reported at AHA 2010) examined the role of PFO closure for first time stroke/TIA and found no difference in the composite primary end point of stroke or TIA at 2 years, all-cause 30-day mortality, and neurologic mortality between 31 days and 2 years, with closure compared with aspirin, warfarin, or both. There are several other ongoing trials that are comparing percutaneous PFO closure with medical therapy. These include the CLOSE trial, the PC-Trial, the RESPECT trial, and the REDUCE trial. In general, device closure should be mainly performed in patients with recurrent cryptogenic stroke despite aggressive medical therapy. The same devices utilized for ASD closure are generally used to percutaneously close PFO. Contraindications to percutaneous closure are noted in Table 29.2.

Primary surgical closure of PFO is generally not pursued, unless the patient needs concomitant surgery for other conditions. Indiscriminant repair of PFO incidentally found at surgery may actually increase short-term stroke risk and should therefore be avoided.

There is a dearth of data to support PFO closure in patients with migraine headaches. The MIST (Migraine Intervention with STARFlex Technology) trial randomized 147 participants with severe migraine headaches and right-to-left shunt consistent with PFO to either percutaneous closure or sham procedure. After 6 months, there was no statistically significant difference in the primary end point of complete cessation of migraine headache or in a host of secondary end points including change in severity, quality, and frequency of headache as well as quality of life. As such, device closure should only be performed in migraine patients who are part of a randomized clinical study.

Patients with platypnea-orthodeoxia syndrome (acute arterial desaturation with change in position from supine to upright) should be considered for closure, as oxygen saturation generally improves with successful elimination of the right-to-left shunt.

ACKNOWLEDGMENTS: *The authors would like to gratefully acknowledge the contributions of Kellan Ashley, Niranjan Seshadri, and J. Donald Moore to previous editions of this manuscript.*

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CHAPTER

30

Christopher H. May

Ventricular Septal Defect

I. Introduction

- A. Ventricular septal defect (VSD) is one of the most common congenital heart defects in both children and adults. The prevalence in neonates has been reported to be as high as 5% when screened with color Doppler echocardiography, although most of these are miniscule defects that close spontaneously within the first year. Thus the true prevalence is difficult to ascertain, given that many defects close spontaneously

and patients are frequently asymptomatic with smaller lesions. VSDs are frequently associated with other congenital defects, particularly infundibular stenosis or valvar pulmonary stenosis. Isolated VSDs account for about 20% to 25% of all congenital heart defects in childhood. Unlike many other congenital abnormalities, males and females appear to be affected equally.

- B. Isolated VSDs are found in approximately 10% of adult patients with congenital heart disease. This reflects the natural tendency for spontaneous closure during infancy and an improved ability to confirm the diagnosis in childhood, which leads to surgical closure.

- C. **Natural history**

1. **Spontaneous closure** occurs most commonly with smaller, restrictive VSDs, usually before the age of 2 years. In general, nearly 35% of perimembranous defects close spontaneously and 75% to 80% of all small VSDs close spontaneously by 10 years of age. These higher rates of spontaneous closure in more recent series are a reflection of the ability to diagnose much smaller defects with more contemporary echocardiographic modalities. Large and nonrestrictive defects have significantly lower spontaneous closure rates (approximately 10% to 15%); malalignment defects rarely close spontaneously. Defects close by two mechanisms: (1) by muscular septum growth and (2) by “aneurysmal tissue” from a septal leaflet of the tricuspid valve as in the case of perimembranous defects. For VSDs that persist, a restrictive nature can protect the patient from pulmonary vascular injury given the flow-limiting nature of these defects.
2. **Endocarditis** is a risk because of the presence of a high-velocity, turbulent jet into the right ventricle. Endocarditis most frequently involves the septal leaflet of the tricuspid valve apparatus at the point of jet impact. The risk of endocarditis is roughly 4% to 10% for the first 30 years of life. Muscular VSDs have a lower incidence of endocarditis, as the jet is attenuated prior to reaching the tricuspid valve.
3. A large VSD during childhood is typically associated with significant **left-to-right shunt** and eventual development of congestive heart failure. Children with very large defects usually present during infancy or early childhood with signs and symptoms of heart failure and pulmonary hypertension. Patients with moderate-sized VSDs can survive to adulthood before detection. Given the gradual development of symptoms in these patients, they may not present until late in the disease course. In these patients, the excess right-sided flow may lead to pulmonary vascular disease and Eisenmenger physiology if left untreated. As pulmonary vascular resistance increases, the left-to-right shunt changes to a right-to-left flow. The VSD murmur disappears during this transition and is often replaced by the murmur of tricuspid regurgitation. After Eisenmenger physiology has developed, patients rarely survive beyond the fourth decade. Complications in patients with Eisenmenger syndrome include pulmonary hemorrhage, endocarditis, cerebral abscess (from hypoxemia), ventricular arrhythmias, and the complications associated with erythrocytosis. Poor prognostic factors in this population include syncope, congestive failure, and hemoptysis.
4. Risk factors for decreased survival include cardiomegaly seen on the chest radiograph; elevated pulmonary artery systolic pressure (> 60 mm Hg and/or more than one-half of the systemic pressure); cardiovascular symptoms such as shortness of breath, fatigue, or dyspnea on exertion; and progressive aortic insufficiency. Good prognostic factors include normal left ventricular (LV) size and function, small left-to-right shunt, normal pulmonary pressures or resistance, an intact vasodilator response in the pulmonary vasculature, and a lack of symptoms.
5. Genetic factors play a significant role in this disease, as in other forms of congenital heart disease. Having an affected father increases the risk of VSD in

the offspring to 2%; moreover, an affected mother appears to confer an even higher risk of recurrence in offspring—as high as 6% to 10%. In general, VSDs arise due to a combination of polygenic, multifactorial abnormalities. However, several monogenetic abnormalities leading to VSDs such as mutations in the transcription factors TBX5 and GATA4 have recently been described.

II. ANATOMY

A. Embryology. Partitioning of the ventricular mass begins as a muscular ridge in the floor of the ventricle near the apex. This ridge later undergoes active growth, which forms the muscular ventricular septum. Concomitantly, the endocardial cushions fuse and the two regions meet, completing closure of the interventricular foramen. Figure 30.1 shows anatomic localization of VSDs.

B. Defect size. The consequences of a VSD depend on the size of the defect and the pulmonary and systemic vascular resistances. Smaller defects provide higher resistance to flow and will have little impact on right-sided flow. **The VSD is described as small** when the defect size is **less than one-third of the size of the aortic root**, **moderate** when the defect size is **less than one-half of the size of the aortic root**, and **large** when the defect size is equal to or **larger than the size of the aortic root**. However, other indirect measures, including clinical signs and symptoms and echocardiographic features, must be taken into consideration when determining the size and clinical significance of a VSD. VSD size is often classified on the basis of its hemodynamic consequences:

- 1. Restrictive** VSDs result in a significant pressure gradient between the left and right ventricles (e.g., pulmonary/aortic systolic pressure ratio < 0.3) and are associated with a small shunt ($Q_p/Q_s \leq 1.4:1$).
- 2. Moderately restrictive** VSDs produce an intermediate interventricular gradient and result in a moderate shunt ($Q_p/Q_s = 1.4$ to $2.2:1$).
- 3. Nonrestrictive** VSDs are usually larger than 1 cm^2 and are associated with a large shunt ($Q_p/Q_s > 2.2:1$). The pressures in the left ventricle and right ventricle will eventually approach equalization, and the amount of flow across the defect will be determined by the ratio of pulmonary-to-systemic vascular resistance.

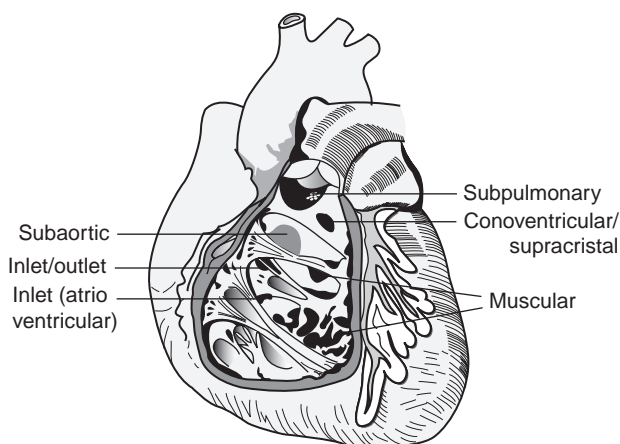


FIGURE 30.1 Anatomic localization of ventricular septal defects.

C. VSD types

1. **Membranous** defects are the most common type, accounting for approximately **70% to 80% of VSDs**. The membranous septum is the area under the aortic valve on the left side and next to the septal leaflet of the tricuspid valve on the right side. Most of these defects extend into the infundibular region and are then referred to as perimembranous. **Membranous defects** are less likely to be associated with additional intracardiac defects and **have a high rate of spontaneous closure**. However, when there is malalignment of the defect, spontaneous closure is unlikely.
 2. **Muscular** defects account for approximately 5% to 20% of VSDs and can be single or multiple (i.e., Swiss cheese septum). These defects, when single, also have a high spontaneous closure rate.
 3. **Inlet or atrioventricular (AV) canal-type** defects account for approximately 5% to 8% of cases. These defects rarely close spontaneously, are usually large, and are associated with abnormalities of the AV valves. These abnormalities range from cleft mitral and tricuspid valves to the common AV valve, as seen in complete AV canal defect. This type of defect in the inlet ventricular septum is commonly seen in patients with Down syndrome (Trisomy 21).
 4. **Supracristal or subaortic** defects account for approximately 5% to 7% of cases and are located immediately beneath the pulmonary and aortic valves. These defects vary in size but are often small. Because of their **proximity to the aortic valve, aortic leaflet tissue can invaginate and result in their closure, with the unfortunate result of significant aortic regurgitation**.
- D. Associated lesions.** Approximately 20% of VSDs are associated with many other forms of congenital heart disease, including aortic coarctation, bicuspid aortic valve, and patent ductus arteriosus. Of patients who present with a VSD, 5% to 10% will develop aortic regurgitation because of poor support of the right coronary cusp and the Venturi effect caused by the VSD jet, resulting in prolapse of one of the aortic valve leaflets. Discrete, fibrous subaortic stenosis and right ventricular (RV) outflow tract obstruction are less common associations. Less than 10% develop subvalvular pulmonary stenosis or an obstructive muscle bundle referred to as a double-chamber right ventricle. VSD is also associated with transposition of the great arteries, tetralogy of Fallot, and Trisomies 13, 18, and 21.

III. CLINICAL PRESENTATION. Adult presentation occurs most frequently in small, restrictive VSDs and occasionally occurs in patients with moderate lesions and associated pulmonary hypertension or with Eisenmenger syndrome in large, unoperated lesions.

- A. Symptoms.** The most common symptoms in adult patients with hemodynamically significant VSD are dyspnea on exertion and exercise intolerance. The symptoms are related to the degree and chronicity of left-to-right shunt and the resultant increase in pulmonary pressure and resistance.
- B. Physical findings.** The auscultatory findings classically include a holosystolic murmur of varying intensity. Smaller muscular defects may produce a high-frequency early systolic murmur that ends before the second heart sound (S_2) because of closure from muscular contraction of the septum. The pitch of the murmur can be a clue to the size and nature of the defect. Smaller and more restrictive defects produce higher pitched and louder murmurs that may be associated with a palpable thrill. Another important feature is the intensity of the pulmonary component of S_2 , which if increased suggests increased pulmonary pressure. An RV heave may be appreciated in patients with RV volume overload. A diastolic flow rumble at the apex may be heard in large left-to-right shunts due to increased flow across an otherwise normal mitral valve. Depending on associated lesions, other findings may be present such as a diastolic murmur of aortic insufficiency that may occur with

subaortic defects. A prominent systolic ejection murmur at the left upper sternal border suggests subvalvular pulmonic stenosis or double-chamber right ventricle. As pulmonary hypertension and right-to-left shunting develop, other signs including cyanosis, elevated jugular venous pressure, enlarged and pulsatile liver, clubbing, and a decrease in murmur intensity may occur. A systolic murmur in this setting often reflects concomitant tricuspid insufficiency. Notably, the murmur of a large VSD is often less harsh and more blowing in nature than that of a small VSD because of the absence of a significant pressure gradient across the larger defect which results in less turbulent flow.

- C. The **differential diagnosis** on examination includes tricuspid regurgitation, acyanotic tetralogy of Fallot with a pulmonary outflow murmur, isolated subvalvular pulmonic stenosis, and hypertrophic cardiomyopathy.

IV. LABORATORY TESTS

- A. The **electrocardiogram (ECG)** may be unremarkable with small defects or reveal left atrial and LV enlargement in patients with larger defects. An inlet or AV canal defect can be diagnosed from the ECG based on the presence of marked left-axis deviation. Right-axis deviation suggests elevated RV and pulmonary artery pressure. After surgical repair, right bundle branch block may occur.
- B. A **chest radiograph** is often helpful in determining the degree of left-to-right shunt. A small-sized or normal-sized heart with normal pulmonary vascular markings on the chest radiograph suggests a hemodynamically insignificant lesion, whereas cardiomegaly and left atrial and LV enlargement are seen with large left-to-right shunts. A large defect associated with a small heart and oligemic lung fields should raise the suspicion of pulmonary vascular disease.

V. DIAGNOSTIC TESTING

- A. **Echocardiography** is the diagnostic modality of choice for VSDs and associated lesions. Transthoracic echocardiographic imaging is almost always sufficient in the child and young adult, but transesophageal echocardiographic imaging may be required in some older adult patients. Defect size and location should be defined using two-dimensional and color Doppler techniques. Complete scans of the ventricular septum should be made to rule out additional defects. Optimal images are usually obtained from the parasternal long-axis and short-axis views and the apical four-chamber view; other views may fail to visualize the VSD jet, owing to perpendicular alignment of the echocardiographic probe and the jet. In the younger patient, subcostal coronal and sagittal views may also be helpful. Measurements of left atrial and LV size are key to determining the amount of volume load and magnitude of the left-to-right shunt. Echocardiographic features of pulmonary hypertension are helpful in confirming the impending reversal of shunt. Quantification of shunt velocity provides an estimate of the restrictive nature of the defect. Higher velocities indicate a more restrictive defect, reducing the likelihood that the patient has experienced pulmonary vascular insult. Systemic blood pressure should be noted when the velocity across the VSD is measured. Assuming no LV outflow obstruction, RV pressure can then be estimated based on the gradient across the VSD. This pressure can also be estimated if tricuspid insufficiency exists. A **perimembranous VSD** can be associated with a **ventricular septal aneurysm formed by the septal leaflet of the tricuspid valve bowing into the defect**. Similarly, supracristal VSDs are associated with aortic insufficiency caused by prolapse of the right or left coronary cusps into the VSD. A complete evaluation is always indicated to exclude other associated findings such as aortic coarctation, atrial septal defect, patent ductus arteriosus, and RV or LV outflow tract obstruction.

- B. Catheterization** is seldom needed in the management of isolated VSD in the infant or child. Surgical correction, when indicated, proceeds in most cases based on echocardiographic evaluation. In the adult, catheterization should be considered if anatomic questions remain despite transthoracic and transesophageal echocardiography or if pulmonary hypertension is suspected based on these studies. Hemodynamic assessment should include quantification of cardiac index and careful oximetric definition of the shunt level and quantity. A step-up in saturation measured at the pulmonary artery level confirms persistent left-to-right shunt across the defect and should correlate with acceptable pulmonary artery pressures and resistance. Evidence of low pulmonary artery saturations is expected with elevations of pulmonary resistance. Simultaneous comparison of RV pressure with systemic pressure is mandatory in these cases, along with the documentation of changes in response to oxygen or nitric oxide administration. Left ventriculography performed with **left anterior-oblique and cranial angulation** demonstrates the defect in most cases. If an inlet-type defect is present, the hepatoclavicular view (about 40° left anterior-oblique and 40° cranial) is usually adequate. Right ventriculography does not adequately opacify the left ventricle unless there is suprasystemic RV pressure. Coronary angiography should be performed when patients are felt to be at risk for coronary artery disease and likely to require operative intervention. Aortography can be helpful in eliminating the possibility of an associated ductus arteriosus or coarctation of the aorta.
- C. Cardiac computed tomography (CT)** can be used to assess VSD anatomy in patients with suboptimal echocardiographic images, but unlike magnetic resonance imaging (MRI), CT does not provide added information about shunt fraction (see Chapter 52) and carries additional risk associated with radiation and intravenous contrast administration.
- D. MRI**, using spin-echo and velocity-encoded cine sequences, can also be used to delineate VSD location and shunt fraction. MRI is particularly helpful in patients with associated complex lesions and those with inadequate echocardiographic images (see Chapter 51).

VI. THERAPY. Factors supporting intervention include cardiomegaly on the chest radiograph, significant left-to-right shunt (pulmonary-to-systemic flow ratios $> 1.5:1$), elevated but responsive pulmonary vascular resistance, symptoms of congestive failure or associated lesions such as aortic insufficiency, RV or LV outflow tract obstruction, and recurrent endocarditis. Management of VSD after myocardial infarction is discussed separately in Chapter 3.

- A. Medical management** in symptomatic cases without Eisenmenger physiology involves anticongestive measures such as the use of diuretics and digoxin. Efforts should then be focused on addressing suitability for surgical closure. Endocarditis is a recognized complication of VSD. In the patient with culture-proven endocarditis, 4 to 6 weeks of antibiotics should be administered parenterally before consideration of intervention. This must be tailored to the individual patient's clinical status and the infective organism's identification and sensitivity as well as the presence of concomitant valvular lesions and prosthetic material. For patients who have developed elevated pulmonary vascular resistance, selective pulmonary vasodilators, including phosphodiesterase-5 inhibitors, prostacyclin analogs, and endothelin receptor antagonists, may improve hemodynamics and exercise tolerance (see Chapter 32).
- B. Transcatheter device closure** of VSDs is being performed on an investigational or compassionate-use basis in selected medical centers. The Amplatzer Muscular VSD Occluder is FDA approved and can technically close many muscular defects. Perimembranous defects, however, pose particular problems for transcatheter closure given their close proximity to the conduction system and the AV and semilunar valves, although recent data from the investigational Amplatzer Membranous

VSD Occluder are promising. Although long-term data from these devices are lacking, recent studies show that the rate of complete closure for the Amplatzer membranous device at 6 months is 96% and is 100% for the muscular occluder at 3 to 96 months follow-up. Complications with these devices include early or late-onset complete heart block, arrhythmia, tricuspid valve damage resulting in stenosis or regurgitation, and mechanical device failure during deployment. Transcatheter closure of VSDs after ventricular septal rupture in the setting of myocardial infarction has also been performed in selected individuals who are considered high-risk surgical candidates. Surgery, however, is still the preferred treatment modality in this setting.

- C. **Surgical closure** continues to be the primary means of defect repair. Outcomes after VSD closure are good in children, with low mortality rates of 2% to 3%. Repair of VSDs in patients with evidence of increased pulmonary artery pressure is generally performed before the age of 2 years and, in many centers, in the first year of life. Surgical closure in the symptomatic adult appears to be well tolerated, with acceptable mortality and improved functional status. Irreversible pulmonary vascular disease with Eisenmenger physiology, however, is a general contraindication for surgical closure because right heart failure will often develop thereafter. Pulmonary artery banding (performed to limit pulmonary blood flow) was more frequently done in the past and is now reserved for the few patients who are very small, have lung disease, or who have complex, multiple VSDs. Postoperative sequelae include residual patch leaks, as well as supraventricular and ventricular arrhythmias. More recent studies have shown the presence of a residual shunt following surgical closure in 5% to 31% of patients depending on the type of VSD that was repaired. Recent data suggest that postsurgical residual VSDs < 2 mm close spontaneously within 1 year in the majority (83%) of patients.
- D. In children for whom transcatheter and surgical approaches are technically difficult or particularly high risk, a **hybrid approach** has been explored. In these patients, a sternotomy is performed, and the device is placed through the anterior wall of the right ventricle under fluoroscopic and echocardiographic guidance.
- E. According to the American Heart Association (AHA) guidelines, **antibiotic prophylaxis** is recommended in three situations in relation to congenital heart disease: (1) unrepaired cyanotic defect (i.e., VSD with right-to-left shunt), (2) repaired defect (i.e., VSD) with prosthetic material/device for the first 6 months, and (3) repaired defect (i.e., VSD) with residual defect at the site of a prosthetic patch/device. In addition, excellent oral hygiene and regular dental examinations are an important component in reducing the risk of developing infective endocarditis.
- F. **Eisenmenger syndrome** is usually referred to in the context of **irreversible pulmonary hypertension from long-standing exposure of the pulmonary vasculature to left-to-right shunting** across a VSD. However, this physiology can occur as a result of any left-to-right shunt, including patent ductus arteriosus and, less commonly, isolated atrial septal defect. As a result of the elevated pulmonary pressures, the direction of shunting is reversed across the defect, producing systemic cyanosis and its associated complications. As described above, newer agents aimed at decreasing resistance in the pulmonary vasculature may be beneficial in these patients. **Pregnancy is poorly tolerated and is contraindicated in the presence of Eisenmenger syndrome** (see Chapter 38).
- G. Long-term follow-up is required in patients whose VSDs were repaired later in life, since the majority of patients already have some degree of pulmonary hypertension, LV dysfunction, or both. Patients with residual shunt after repair, arrhythmias, or conduction blocks also require continued follow-up.

ACKNOWLEDGMENTS: *The author thanks Drs. J. Donald Moore, Matthew Hook, and Samuel Unzek for their contributions to earlier editions of this chapter.*

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Patent Ductus Arteriosus and Coarctation of the Aorta

I. PATENT DUCTUS ARTERIOSUS—INTRODUCTION

- A. The ductus arteriosus is a fetal communication between the descending aorta just distal to the left subclavian artery and the main pulmonary artery near its bifurcation. A patent ductus arteriosus (PDA) occurs when the ductus arteriosus fails to close and regress after birth to form the ligamentum arteriosum. PDA occurs in approximately 1 of 2,000 live births, but it is relatively uncommon among the adult population. In infants, it accounts for 10% to 12% of all congenital heart disease.
- B. **Natural history.** The natural history depends on the size of the PDA, the direction of the shunt, and the development of any associated complications. At birth, 95% of patients with isolated PDA have left-to-right shunts and normal, or near-normal, pulmonary pressures. Patients with normal pulmonary artery pressures and no evidence of chronic left ventricular volume overload have a better prognosis. If untreated, life expectancy of patients with PDA is shortened; one-third of patients with PDA die by the age of 40 and almost two-thirds die by the age of 60. With a PDA, **congestive heart failure (CHF) can occur** because of chronic left heart volume overload. In patients with death related to PDA, CHF is the most common cause. Development of right-to-left shunting is also an ominous sign because it reflects the development of advanced pulmonary vascular disease and associated elevation in right-sided cardiac pressures (see Chapter 32 for discussion on Eisenmenger's syndrome).
- C. **Risk factors.** Factors that increase risk for PDA include maternal rubella infection, birth at high altitude, premature birth, female sex, and genetic factors. In infants born at < 28 weeks of gestation, there is a 60% incidence of PDA. PDAs are twice as common in female infants as in male infants and in some instances have a genetic component. In a family in which one child has a PDA, there is approximately a 3% risk of having a PDA in subsequent offspring.

II. ANATOMY AND PATHOPHYSIOLOGY

- A. **Embryology.** The ductus arteriosus is a **normal and essential component** of cardiovascular development that originates from the distal sixth left aortic arch. A PDA is most commonly funnel shaped with the larger aortic end (ampulla) distal to the left subclavian artery, then narrowing toward the pulmonary end, with insertion at the junction of the main and left pulmonary arteries. The Krichenko classification system describes the angiographic appearance of PDA (Table 31.1). In right-sided aortic arch, the anatomy of PDA can vary significantly: the PDA can arise from the left innominate artery and insert into the proximal left pulmonary artery or arise distal to the right subclavian artery with insertion into the proximal right pulmonary artery. Bilateral PDAs can also occur.
- B. **Fetal circulation.** The presence of the ductus arteriosus in the fetal circulation is essential to allow **right-to-left shunting of nutrient-rich, oxygenated blood**

TABLE 31.1 Krichenko Classification of Patent Ductus Arteriosus Appearance on Angiography

Type A	Conical	Well-defined aortic ampulla and constriction near pulmonary insertion
Type B	Window	Short, with narrowing near aortic insertion
Type C	Tubular	Tubular duct without constrictions
Type D	Complex	Multiple constrictions
Type E	Elongated	Long PDA with conical appearance and multiple constrictions

PDA, patent ductus arteriosus.

from the placenta to the fetal systemic circulation, thereby bypassing the fetal pulmonary circuit. In the normal fetal circulation, oxygenated blood travels from the mother through the placenta to the fetus. The oxygen-rich blood traverses the fetal inferior vena cava, right atrium, right ventricle, and main pulmonary artery. The fetal pulmonary arteries are constricted and have high pulmonary vascular resistance. Oxygenated blood bypasses the fetal pulmonary circulation and enters through the ductus arteriosus to the lower resistance systemic circulation. Oxygenated blood then enters the fetal aorta distal to the left subclavian artery, perfuses the fetal systemic circulation, becomes deoxygenated, and returns to the maternal circulation. **In the fetus, the ductus arteriosus is kept open by low arterial oxygen content and placental prostaglandin E2 (PGE2).**

- C. Birth.** Several **changes occur at birth** to initiate normal functional **closure of the ductus arteriosus within the first 15 to 18 hours of life.** Spontaneous respirations result in increased blood oxygen content. Prostaglandin levels decrease because of placental ligation and increased metabolism of prostaglandins within the pulmonary circulation by prostaglandin dehydrogenase. The combination of increased oxygen content and lowered circulating prostaglandin levels usually results in closure of the ductus arteriosus. Generally, the ductus arteriosus is hemodynamically insignificant within 15 hours and completely closed by 2 to 3 weeks. The **fibrotic remnant** of this structure persists in the adult as the **ligamentum arteriosum.** **Spontaneous closure of a PDA is unlikely in term infants after 3 months and in preterm infants after 12 months.**

III. CLINICAL PRESENTATION

- A. Symptoms.** Severity of symptoms depends on the degree of left-to-right shunting; and it is determined by the size of the PDA, ductal resistance, cardiac output, as well as the systemic and pulmonary vascular resistances. PDA size is categorized by the degree of left-to-right shunting determined by the pulmonary-to-systemic flow ratio: $Q_p:Q_s$ (Table 31.2). Between 25% and 40% of patients with PDA are asymptomatic, especially those with a small PDA. They are often diagnosed by auscultation

TABLE 31.2 Patent Ductus Arteriosus Size by $Q_p:Q_s$

$Q_p:Q_s$	Size
< 1.5	Small
1.5–2.2	Moderate
> 2.2	Large

of a continuous murmur on examination or incidentally during diagnostic testing. With larger PDAs, symptoms may develop. The most common symptom is exercise intolerance followed by dyspnea, peripheral edema, and palpitations. As is often the case in adult congenital heart disease, a previously well-tolerated PDA may become manifest in the setting of acquired heart disease such as ischemia, essential hypertension, and valvular disease.

- B. Physical examination.** Patients with PDAs may present with a wide range of physical findings. Pulse pressure may be wide because of diastolic runoff into the PDA, and peripheral pulses may be bounding. The jugular venous pressure is often normal with a small PDA, whereas with a large PDA, prominent a and v waves may be present. Precordial palpation often reveals a normal precordial impulse with a small PDA and a prominent left ventricular impulse with a large PDA. A **harsh, continuous murmur may be heard at the left first or second intercostal space**. The murmur envelops the second heart sound (S_2) and decreases in intensity during diastole. A small PDA has a soft, high-frequency, continuous murmur, whereas a large PDA classically has a machinerylike, loud murmur. With a large PDA, a middiastolic apical murmur may occur because of increased diastolic flow across the mitral valve. If **pulmonary hypertension** is present, a right ventricular lift may be present and the pulmonic component of S_2 will have increased intensity. The duration of the diastolic murmur reflects pulmonary artery pressures; elevated pulmonary artery pressures lead to a decreased gradient for left-to-right flow through the PDA during diastole, which results in a shorter diastolic murmur. As pulmonary pressure increases, the systolic component of the murmur shortens. Right-to-left flow may not generate a systolic murmur. For patients with a right-to-left shunt, a pathognomonic physical finding is **differential cyanosis of the lower extremities and left hand**.
- C. Complications.** The most common complications of PDA include **CHF, infective endocarditis**, and **pulmonary hypertension**. CHF occurs through volume overload of the left side of the heart and may be accompanied by **atrial fibrillation**. Vegetations generally develop on the pulmonary side of the PDA, and septic lung emboli may occur. Untreated PDAs with audible murmurs have a risk of infective endocarditis of 0.45%/y after the second decade. Spontaneously occurring **aneurysms of the ductus arteriosus** have been reported, although they are typically seen in association with endarteritis or among very young or very old patients. Pulmonary hypertension develops as a result of increased pulmonary vascular flow from a large PDA with significant left-to-right flow. Elevation in right-sided pressures may eventually result in Eisenmenger's physiology, right-to-left flow, and isolated cyanosis and clubbing of lower extremities (occurring in 5% of unrepaired PDA patients) with signs of pulmonary hypertension.
- D. Differential diagnosis.** The differential diagnosis of PDA includes ventricular septal defect associated with aortic insufficiency, aortopulmonary window, pulmonary atresia with systemic collateral vessels, innocent venous hum, and arteriovenous communications such as pulmonary arteriovenous fistula, coronary artery fistula, systemic arteriovenous fistula, and ruptured sinus of Valsalva aneurysm.

IV. LABORATORY TESTING

- A. Hematology.** Blood laboratory results are generally unremarkable, although compensatory erythrocytosis may be present in the setting of long-standing cyanosis resulting from a right-to-left shunt.
- B. Electrocardiogram (ECG).** ECG is neither sensitive nor specific for PDA. The ECG for a patient with a small PDA is often normal. Depending on the duration and hemodynamic significance of the PDA, electrocardiographic criteria for left atrial enlargement or left ventricular hypertrophy may be present. If pulmonary hypertension exists, the ECG may demonstrate right ventricular hypertrophy or right atrial enlargement.

- C. Chest radiography (CXR).** CXR is neither sensitive nor specific for PDA. A normal chest radiograph implies a small, hemodynamically insignificant PDA. With a large PDA, left atrial and left ventricular enlargement may be present, as well as increased pulmonary vascularity. With right-to-left shunting from pulmonary hypertension, the main pulmonary artery is frequently enlarged. The PDA occasionally appears as a separate convexity between the aortic knob and the pulmonary trunk. Calcification of the PDA may be visualized in older individuals.

V. DIAGNOSTIC TESTING. Standard transthoracic echocardiography (TTE) is the preferred initial diagnostic modality because of its low cost and noninvasive nature. Transesophageal echocardiography (TEE) may be required in subjects with suboptimal echocardiographic windows. Cardiac catheterization is typically reserved for therapeutic intervention.

- A. TTE** has a 42% sensitivity and 100% specificity for the diagnosis of PDA. The suprasternal notch view is usually best for demonstrating the PDA, particularly its aortic origin. The complete course of a PDA may be difficult to follow in some patients because of its tortuosity. Color Doppler imaging can often reveal flow between the descending aorta distal to the left subclavian artery and the pulmonary trunk. It is imperative to demonstrate color Doppler flow within the pulmonary artery, typically on a high parasternal short-axis view. Color Doppler and continuous wave Doppler help determine the direction of flow in the PDA. The timing of flow (systolic or diastolic) depends on pressure gradients between the systemic and pulmonary circulation. Quantitative assessment of shunt velocity is valuable to estimate the degree of restriction across the PDA. This measurement becomes important when planning transcatheter intervention. Diastolic aortic flow reversal is seen in the descending aorta if the shunt is significant. Associated left atrial and left ventricular enlargement also suggest a hemodynamically significant lesion.
- B. TEE** may be required if TTE windows are suboptimal or nondiagnostic. TTE and TEE have nearly 100% specificity for the diagnosis of PDA, but TEE has a much higher sensitivity (97%) than TTE (42%).
- C. Cardiac catheterization** is rarely needed for diagnostic purposes. Rarely, PDAs undiagnosed by physical examination or noninvasive testing may be diagnosed during left heart or right heart cardiac catheterization by recognizing the unexpected course of the catheter as it crosses the PDA by measuring a step-up in the oxygen saturation at the level of the left pulmonary artery or by documenting pulmonary opacification by descending aortography.
1. A PDA is best demonstrated by a **descending aortogram** performed in the **lateral projection** with a standard angiographic catheter positioned just below the ductal ampulla. If biplanar imaging is used, the right anterior–oblique cranial projection is sometimes helpful.
 2. A PDA can be crossed from the main pulmonary artery or from the descending aorta, with the latter being easier and best guided by the lateral projection. Oximetric sampling typically demonstrates an increase in saturation in the main pulmonary artery compared with the right ventricle. Pulmonary artery and right ventricular pressures may be slightly elevated but typically remain below systemic levels. The etiology is usually pulmonary arterial vascular disease, but it can also be due to pulmonary venous stenosis, mitral stenosis, or left ventricular failure. The presence of systemic pulmonary pressures generally indicates severe and advanced pulmonary vascular disease.
- D. Magnetic resonance imaging (MRI) and computed tomography** may be useful in defining the anatomy in patients with unusual PDA geometry and in patients with associated abnormalities of the aortic arch.

VI. THERAPY. ACC/AHA 2008 guidelines for adults with congenital heart disease recommend closure of PDA (catheter or surgical) if there is **left atrial or left ventricular**

enlargement or if pulmonary arterial hypertension (PAH) is present with net left-to-right shunt (class I); or of an **asymptomatic small PDA by catheter device** (class IIa). PDA closure is **contraindicated** in patients with **PAH and right-to-left shunt**. Successful closure of PDA generally results in a good prognosis and may prevent adverse left ventricular remodeling resulting from volume overload.

The shape and size of a PDA determine the mode of therapy. Small- or moderate-caliber PDAs are generally closed percutaneously with coils. Large PDAs may require the Amplatzer Duct Occluder (ADO) or surgery. Heavily calcified PDAs represent a relative contraindication to surgical closure because of an increased risk of bleeding and incomplete closure with surgery. Cardiopulmonary bypass may be required for heavily calcified PDAs. PDAs with significant right-to-left shunts and Eisenmenger's physiology should generally not be closed. In patients with pulmonary vascular resistance $> 8 \text{ U/m}^2$, lung biopsy has been recommended to determine candidacy for closure. However, even histologically severe pulmonary vascular disease may resolve after closure of the PDA. Reactivity of the pulmonary vascular bed to pulmonary vasodilating agents or significant reduction in pulmonary artery pressure during test occlusion may signal reversibility of pulmonary hypertension, but the absence of these findings does not rule out the possibility of reversibility in the long-term and natural history may be significantly altered by treating with pulmonary vasoactive medications.

A. Since the early 1990s, **transcatheter techniques** have become the **first-line therapy for most PDAs**. Many centers use single or multiple stainless steel coils to achieve complete closure. Numerous devices have been adapted or are under clinical investigation to allow transcatheter closure of larger defects. These procedures can often be performed on an outpatient basis, and complete closure rates at follow-up generally exceed 90% to 95% in most studies. The mortality rate is typically $< 1\%$ at experienced centers. Success has been reported even when ductal calcification has been apparent, but large clinical series are lacking.

1. **Percutaneous coil occlusion.** Percutaneous coils were developed in 1992 and are the **preferred treatment for older children and adults with PDAs $< 3.5 \text{ mm}$ in diameter**. Embolization coils have thrombogenic strands spanning the coils and are placed across the PDA to occlude flow. Advantages include low cost, small-caliber venous access, and easy implantation. Advances include detachable coils and development of a snare-assisted technique, both of which allow assessment and fine-tuning to ensure correct coil position before actual release of the coil. The coils are loaded at the tip of a catheter, the catheter is placed in the PDA under fluoroscopic guidance, and the coils are then deployed. Selected coil sizes are 2 to 2.5 times the narrowest diameter of the PDA. With moderate-sized or large-sized PDAs, multiple coils may be used. However, as PDA size becomes larger (> 3.5 to 4.0 mm), percutaneous, $0.038''$ coils become a less desired closure option, and alternative therapies become preferred. Although complete closure is usually accomplished with a single coil in children, multiple coils are frequently needed for complete closure in the adult. Although coil embolization may occur, the snare-assisted technique is almost always successful at percutaneous removal of the coil.
2. The **ADO**, a cone-shaped plug occluder made of thrombogenic wire mesh delivered with a 5F to 7F venous system, is the **preferred device for percutaneous closure of moderate to large PDAs**. The ADO stents the PDA, and blood is forced to flow through the center of the device, which is lined with thrombogenic wire mesh. The PDA then essentially clots off. Advantages include simple implantation, ability to retract the ADO into the sheath and redeploy if needed, and high success rates. There is an 89% occlusion rate on postprocedure day 1 and 97% to 100% complete occlusion after 1 month.
3. **Complications** of transcatheter closure are rare. The most common complication is embolization of the coil or device. Embolized coils can usually be retrieved; but even when this is impossible, adverse consequences are rare. Other

potential complications include flow disturbance in the pulmonary artery or aorta from device protrusion, hemolysis from high-velocity residual shunting, vascular access complications, and infection.

- B. Surgical closure.** In 1938, the first successful closure of a PDA was performed, which, coincidentally, was the first repair of a congenital heart defect. Surgical closure is the most effective method for complete closure and is usually performed without cardiopulmonary bypass by double ligation and division of the PDA. Ligation may be performed without division, but there is a risk of recanalization of the PDA in up to 20% of cases. In neonates and premature infants, ligation without division is performed because of the small size of the structures. With continued advances in percutaneous closure devices, **surgery has become second-line therapy for most adults with PDAs**. If surgery is necessary, the procedure is > 95% successful and has a low complication rate. The operative mortality rate is < 1%. However, the thoracotomy approach can be painful for adults and necessitates inpatient recovery. Newer surgical techniques such as transaxillary thoracotomy and video-assisted thoracoscopic ligation have improved surgical morbidity.
- C. Medical therapy.** In adults, medical therapy is ineffective to close a PDA. Medical therapy is indicated to prevent and treat complications of PDA, including heart failure, atrial arrhythmias, and pulmonary hypertension. **The most recent guidelines from the American Heart Association (AHA)** recommend antibiotic prophylaxis for endarteritis only in the setting of transcatheter closure of the PDA for 6 months after the procedure; and prophylaxis is not recommended for those with repaired PDA without residual shunt.
- D. Follow-up.** If immediate duct closure is demonstrated after the procedure, a 6-month follow-up with TTE should suffice to assess for residual flow through the PDA. If residual shunt exists after the procedure, TTE should be performed every 2 to 3 months and early repeat attempt of complete closure considered, depending on the size of the residual shunt or the presence of hemolysis. For long-term follow-up, annual transthoracic echocardiograms are adequate.

VII. COARCTATION OF THE AORTA. Coarctation of the aorta (CoA) has been found at autopsy in approximately 1 in every 1,550 individuals. It accounts for 5% to 10% of congenital heart disease and occurs more frequently in whites (7:1) and males (2:1). The disorder is typically diagnosed in childhood but may go undetected well into adulthood. Most patients develop persistent systemic hypertension, often as children, and are at risk for premature coronary artery disease. Cases usually occur sporadically, but an autosomal-dominant inheritance pattern has been observed. It is frequently associated with bicuspid aortic valve, and coarctation should be excluded in patients with bicuspid aortic valve and hypertension. Coarctation also occurs in 15% to 35% of patients with Turner's syndrome. Potential catastrophic complications include aortic rupture or dissection and cerebral berry aneurysm rupture. The mean survival for unrepaired patients is 35 years, with a 25% survival rate beyond 50 years.

VIII. ANATOMY. CoA usually consists of a **narrowing in the region of the ligamentum arteriosum**, the remnant of the ductus arteriosus, just distal to the origin of the left subclavian artery. Most coarctations, therefore, are juxtaductal. The exact anatomy, however, varies, and the coarctation may include a long segment, the transverse arch, or the abdominal aorta. Rarely, tortuosity of the arch is identified. The main anatomic substrate is a prominent posterior shelf of the aorta, composed predominantly of thickened media.

- A. Embryology.** The exact embryonic origin remains uncertain, but two main theories exist. The first suggests that the narrowing is caused by aberrant ductal tissue

that constricts the aorta at time of ductal closure. The second proposes that aortic hypoplasia develops as a consequence of reduced blood flow in utero.

- B. **Associated cardiac defects** include **bicuspid aortic valve** in 50% to 85% of cases, valvular and subvalvular aortic stenoses, ventricular septal defects, PDA, and congenital malformations of the mitral valve (i.e., smaller orifice, supravalvular ring, and parachute mitral valve resulting from a single papillary muscle). Multiple left-sided heart lesions may be associated with CoA and are often referred to as the **Shone complex**.
- C. **Associated extracardiac defects** include **intracranial aneurysms**, especially within the circle of Willis (3% to 5% of cases), hemangiomas, hypospadias, and ocular defects.

IX. CLINICAL PRESENTATION

- A. **Symptoms.** For patients with CoA who survive to adulthood, symptoms are usually negligible and nonspecific. Patients may complain of headaches, nosebleeds, cool extremities, leg weakness, or claudication with exertion. More serious manifestations include angina and heart failure.
- B. **Physical examination**
 - 1. A thorough cardiovascular examination may identify a systolic ejection murmur at the left upper sternal border that radiates to the intrascapular area located immediately anterior or posterior to the CoA. The murmur may be longer in systole and even continue into diastole, depending on the degree of obstruction. Increased flow through the collateral intercostal arteries can produce a continuous murmur appreciated diffusely over the precordium.
 - 2. Upper extremity hypertension is often present, usually in conjunction with **diminished and delayed femoral pulsations**. CoA should always be considered in the differential diagnosis of refractory hypertension, especially in younger patients.
 - 3. Funduscopic examination may demonstrate a “corkscrew” tortuosity of the retinal arterioles.

X. DIAGNOSTIC TESTING

- A. The **ECG** is frequently normal but may demonstrate manifestations of long-standing hypertension, such as left ventricular hypertrophy and left atrial enlargement.
- B. **Chest radiography.** Cardiomegaly, dilated ascending aorta, and prominent pulmonary vasculature are common. **Rib notching** usually develops by 4 to 12 years of age and is caused by enlarged intercostal collaterals. The **classic “3” or inverted-E sign is pathognomonic** for CoA and is created by a dilated left subclavian artery above the CoA and poststenotic dilation of the aorta below the CoA.
- C. **Echocardiography** is most useful in infants and children. In adults, the suprasternal notch view is most helpful; color Doppler can be used to localize the site of turbulence. Continuous wave Doppler can assess the pressure gradient. If severe narrowing is present, persistence of flow in diastole (widening of the flow profile from systole into diastole) is seen by continuous wave Doppler in the aorta below the coarctation, such as in the abdominal aorta. This is a useful method to ascertain the presence of significant coarctation, even if imaging the direct site of the obstruction is impossible. A complete study should measure left ventricular size and ascending aortic size, determine aortic valve anatomy and function, and identify any potential associated congenital anomalies. TEE can also better define the anatomy if TTE proves inadequate.
- D. **MRI** provides excellent anatomic and hemodynamic information. MRI is increasingly utilized as a first-line investigation before catheterization, particularly in adults. This enables the precise anatomy to be delineated and helps in the decision making regarding surgery or catheterization as treatment options. Serial MRI scans may be

used to follow results of therapeutic procedures. It is also useful in evaluating the intracranial vessels for associated berry aneurysms.

- E. **Cardiac catheterization** provides excellent image data and pressure information and is often more reliable than echocardiography in adults. An **aortic angiogram** in left anterior–oblique or caudal and direct lateral projections usually best defines the lesion. Pressures should be obtained in the left ventricle and the ascending aorta, and the gradient across the lesion should be measured. A **pullback pressure of > 20 mm Hg** signifies hemodynamic significance and usually warrants intervention if concomitant clinical factors allow. A **gradient of > 50 mm Hg** generally mandates intervention. The presence of collateral vessels may falsely diminish the gradient.

XI. THERAPY. Several factors need to be taken into account when deciding on optimal therapy for CoA, including the age of the patient, the anatomy of the coarctation, any prior CoA operations, and the local surgical expertise. Whatever mode of treatment is chosen, the presence of postprocedural upper extremity hypertension influences survival.

- A. In general, **medical therapy** for CoA has very limited utility, but it may be useful in a supportive role along with mechanical treatment. Hypertension should be medically treated, with the goal of controlling blood pressure and preventing end-organ damage.

B. Percutaneous management

1. **Percutaneous balloon angioplasty** is generally less effective than surgery for treatment of primary coarctation. Neonates and infants treated with angioplasty experience high rates of recurrent CoA (about 50% to 60%) and aneurysm formations (5% to 20%); therefore, surgical repair is preferred in this patient population. Likewise, balloon angioplasty of the unoperated coarctation in adults is controversial, with data suggesting higher rates of restenosis and aneurysm formation compared with surgical repair. Procedural complications can include acute aortic rupture (rare), aortic dissection, femoral artery trauma, recurrent coarctation (8%), and aneurysm formation (8% to 35%). The suspected mechanism for late aneurysm formation is intimal tear at the site of cystic medial necrosis within the coarctation site. It should be noted that the clinical impact of aneurysm formation is unclear, as most defects are small and have a low risk of rupture. Percutaneous angioplasty, however, is the preferred therapy for recurrent postsurgical coarctation. The procedure is successful in reducing the gradient to < 20 mm Hg in approximately 80% of interventions, with only a 1.5% incidence of late aneurysm formation.

2. **Stent implantation.** Theoretically, stent implantation may mitigate the development of aneurysm or dissection for a few reasons. By apposing the torn intima to the media and through dispersion of force, stenting may limit vascular trauma. It can also oppose the vascular recoil of the coarcted segment and avoid overdilation. By allowing the use of smaller balloons and graded inflations in staged procedures, stents may also reduce rates of aneurysm formation. Early and intermediate outcomes are promising, with a good safety and efficacy profile as well as lower rates of restenosis and aneurysm formation compared with balloon angioplasty. Despite the lack of long-term outcome data, stenting has become the preferred treatment modality in adults and adult-sized adolescents with native CoA. For recoarctation, balloon angioplasty with or without stenting is preferred in adults as well, as long as the anatomy is suitable.

- C. **Surgery** remains the therapy of choice in neonates and infants. Three types of surgical repair have been used for correction of CoA: resection of the stenosed segment with end-to-end anastomosis, use of a subclavian flap, and patch aortoplasty. The approach with the best long-term outcome and sustained resolution of obstruction has been resection of the stenosed segment with end-to-end anastomosis. This approach carries with it the lowest risk of recurrent CoA (3%) and late aneurysm

formation (rare). Paradoxical hypertension and bowel ischemia may occur in the postoperative period. Major surgical complications include paraplegia caused by perioperative spinal cord ischemia (0.4% to 1%), residual coarctation, aneurysm formation at the site of repair, and, rarely, death. Survival rates of > 90% at 10 years and 84% at 20 years have been reported. Late deaths after surgical repair are related primarily to coronary artery disease, CHF, and aneurysm rupture. Young age favorably influences outcomes after surgery.

XII. FOLLOW-UP. Lifelong follow-up is indicated after the diagnosis of CoA is established, especially after any type of mechanical repair. Key issues to be cognizant of include the progression of hypertension either at rest or with exercise, development of CoA recurrence, aneurysm formation, left ventricular dysfunction, and associated aortic valve dysfunction when bicuspid valve is present. In patients repaired at older ages, hypertension commonly persists despite treatment by percutaneous intervention or surgery. Serial echocardiography is an important component of follow-up. Advanced imaging modalities such as computed tomography or MRI are used increasingly post repair to screen for aortic wall complications, with a preference for MRI given the radiation and contrast issues. Therefore, these patients should be considered “treated” and not “cured” despite repair.

ACKNOWLEDGMENTS: *The authors thank Drs. Michael S. Chen, J. Donald Moore, Adrian W. Messerli, Matthew A. Kaminski, and Arman Askari for their contributions to earlier editions of this chapter.*

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Complex Congenital Heart Disease

- I. TETRALOGY OF FALLOT (TOF).** TOF is the most common form of cyanotic heart disease. It occurs in approximately 1 in 3,000 live births and accounts for 10% of congenital heart disease in infants. It is also the most common congenital heart disease requiring surgical correction in the first year of life. The earliest description of TOF dates back to the 17th century; however, Fallot is credited with describing the classic features of the disease in 1888. Surgical treatment for TOF did not become available until well into the 20th century, and it dramatically improved life expectancy. The **current reparative approach has shifted from palliative shunt procedures to primary surgical repair**, most recently with valve-sparing techniques and usually performed in infancy. Without surgical intervention, only about 10% of patients survive beyond the age of 20 years. Adults with TOF usually have undergone surgical repair or palliation. A wide and complex spectrum of TOF exists including association with pulmonary atresia, absent pulmonary valve, and atrioventricular (AV) canal defects. Classic “simple” TOF is discussed here.

A. Anatomy

- 1. Anterocephalad deviation of the outlet septum** results in four defining features:
 - (a) Right ventricular (RV) outflow tract obstruction
 - (b) Nonrestrictive ventricular septal defect (VSD)
 - (c) Aortic override of the ventricular septum ($> 50\%$ over the right ventricle)
 - (d) Right ventricular hypertrophy (RVH)
- 2. Associated defects.** Anomalous origin of the left anterior descending coronary artery from the right coronary artery (5%) or a prominent conal branch from the right coronary artery can occur. These vessels cross the RV outflow tract. This anatomic feature is important to surgeons because infundibular resection or future conduit placement may be needed in this location and can lead to inadvertent arterial damage. Right aortic arch occurs in 25% of cases. A secundum atrial septal defect (ASD) occurs in 15% of cases, completing the pentalogy of Fallot. Persistent left superior vena cava is found in 5% of patients. Among adult patients, aortic insufficiency can occur naturally from long-term dilation of the aortic root, after endocarditis or as a postoperative sequela. Rare complications include pulmonary hypertension, supraventricular mitral stenosis, and subaortic stenosis. There is an association with deletion in the chromosome 22q11 region, which is also present in DiGeorge syndrome and/or velocardiofacial syndrome.

B. Clinical presentation

- 1. Patients who have not undergone surgical repair** have variable clinical features depending on the amount of RV outflow tract obstruction, degree of aortic override, and, to a lesser extent, systemic vascular resistance, all of which dictate the amount and direction of shunting across the VSD.
 - a.** With severe RV outflow tract obstruction, patients have central cyanosis and clubbing by 6 months of age. Hypoxic “spells” may be seen and are characterized by tachypnea, dyspnea, cyanosis, or even loss of consciousness or

death. If the obstruction is mild, however, the shunt through the VSD may be left-to-right, resulting in “pink tet” with minimal symptoms.

- b. On physical examination, the patient is usually cyanotic and clubbed. A prominent RV impulse may be appreciated because of equalization of right and left ventricular pressures. A lift may be palpated under the right sternoclavicular junction in patients with a right-sided arch. The first heart sound (S_1) is usually normal, but the second heart sound (S_2) is often single because of an inaudible P_2 . Auscultation is notable for a prominent systolic ejection murmur at the left upper sternal border, possibly with an associated thrill. The shorter the murmur, the more severe the infundibular pulmonary stenosis. The murmur of aortic insufficiency may be audible along with an aortic click resulting from a dilated overriding aorta. Continuous murmurs may be heard due to aortopulmonary collateral vessels. The presence of these vessels is more likely in the setting of pulmonary atresia, but they can also be acquired if RV outflow tract stenosis develops gradually.
2. Most adult congenital patients will have undergone surgical repair with or without a prior palliative procedure. The term “**palliation**” (as opposed to “repair”) in these patients refers to a surgical procedure that consists of a **systemic-to-pulmonary artery shunt** (modified Blalock-Taussig shunt, classic Blalock-Taussig shunt, Potts shunt, or Waterston shunt; Table 32.1). These procedures are initially performed to supplement the deficiency of antegrade pulmonary

TABLE 32.1 Index of Postoperative Anatomy among Adult Patients with Congenital Heart Disease

Underlying pathology	Procedure	Notes
Single ventricle Hypoplastic left heart Tricuspid atresia	1. Norwood	Incorporation of native aorta and pulmonary artery (one of which may be hypoplastic or atretic) to produce a “ neo-aorta ” for the single ventricle
Pulmonary atresia with intact ventricular septum Unbalanced complete AV canal defect		Main pulmonary artery is transected from the heart Pulmonary flow is maintained with placement of a Blalock-Taussig shunt Atrial septectomy is often performed to allow complete mixing at the atrial level
	2. Bidirectional Glenn	Usually performed at 4–6 mo if pulmonary arterial anatomy, pressures, and resistances are adequate Anastomosis of the superior vena cava to the pulmonary artery , usually with takedown of a previously placed systemic-to-pulmonary artery shunt and repair of pulmonary arterial branch stenosis if necessary Term <i>bidirectional</i> is used in descriptions of this procedure because both right and left pulmonary arteries usually remain in continuity

TABLE 32.1 Index of Postoperative Anatomy among Adult Patients with Congenital Heart Disease (*Continued*)

Underlying pathology	Procedure	Notes
dTGA (ventriculoarterial discordance)	3. Fontan	Usually performed at 1–5 y depending on growth of vasculature and cyanosis Anastomosis of inferior vena cava to the pulmonary artery by intra-atrial lateral tunnel or extracardiac conduit Pulmonary blood flow is achieved passively, without the assistance of a ventricular pumping chamber
	Rashkind	Atrial balloon septostomy to create mixing of systemic and pulmonary circulation
	Blalock-Hanlon	Surgical atrial septectomy
	Mustard or Senning (atrial switch)	Baffle material (Mustard) or native atrial tissue (Senning) used to direct pulmonary venous blood → right ventricle → aorta; systemic venous blood → left ventricle → pulmonary artery
	Jatene (arterial switch)	Great arteries are transected and reanastomosed to the appropriate ventricle Coronary arteries are removed with a button of surrounding tissue and reimplanted to the appropriate sinuses
Deficient pulmonary artery or RV outflow tract Pulmonary atresia Tetralogy of Fallot with hypoplastic pulmonary arteries	Rastelli	For dTGA with VSD and pulmonary outflow tract obstruction VSD patch closure that directs left ventricular blood across the VSD to the aorta Pulmonary valve is oversewn Valved conduit from the right ventricle to the pulmonary artery to create RV outflow
	Classic Blalock-Taussig	Native subclavian artery anastomosed to the right or left pulmonary artery
	Modified Blalock-Taussig	Expanded polytetrafluoroethylene (Gore-Tex) material connecting the subclavian or innominate artery to the pulmonary artery
	Waterston shunt	Anastomosis between the ascending aorta and right pulmonary artery
	Potts shunt	Anastomosis between the descending aorta and left pulmonary artery

AV, atrioventricular; RV, right ventricular; TGA, transposition of the great arteries; VSD, ventricular septal defect.

blood flow and are taken down at the time of complete repair. The latter two procedures have been abandoned owing to associated uncontrolled pulmonary blood flow and the subsequent development of pulmonary hypertension.

- a. Patients who have undergone palliative repair alone have variable clinical findings depending on the type of palliation performed. In those who have undergone a classic Blalock-Taussig shunt, the brachial pulse on that side may be diminished or absent. If patent, shunts can produce a continuous murmur. Continuous murmurs can also result from aortopulmonary collaterals. Branch pulmonary artery stenosis at prior shunt insertion sites can produce unilateral systolic or continuous murmurs. Systolic ejection murmurs may be audible depending on the degree of antegrade flow across the outflow tract.
3. **Complete (or total) repair** consists of patch closure of the VSD and variable degrees of RV outflow tract resection and reconstruction. It may involve pulmonary valvotomy, RV outflow tract patch augmentation, transannular patch enlargement, or placement of a right ventricle-to-pulmonary artery conduit (i.e., bioprosthetic or homograft). Distal branch pulmonary artery stenosis may have been repaired, or residual lesions may be present. These patients typically have first undergone a palliative shunt procedure, but the current surgical approach has shifted to primary complete repair in infancy.
 - a. Patients are often asymptomatic. They may present with late symptoms such as dyspnea, exercise intolerance, palpitations, signs of right heart failure, or syncope.
 - b. The jugular venous pressure is usually normal unless there is RV dysfunction, in which case elevated jugular venous pressure with a prominent *a* wave is seen. The brisk pulse of aortic insufficiency may also be appreciated. On palpation, there may be an RV lift or a lift under the right sternoclavicular junction when the arch is right-sided. Some degree of turbulence almost always remains across the RV outflow tract and produces a variable systolic ejection murmur at the left upper sternal border, with radiation to the back and peripheral lung fields. Of importance is the presence of associated pulmonary insufficiency. This, even if severe, may occasionally be inaudible due to low-pressure hemodynamics. It is generally appreciated at the left upper sternal border, sometimes producing a to-and-fro murmur together with the outflow tract murmur. A high-frequency systolic murmur at the left lower sternal border suggests the presence of a residual VSD (often due to a small leak in the VSD patch). Continuous murmurs from collateral formation or prior shunts may be appreciated. The diastolic murmur of aortic insufficiency may also be heard.

C. Laboratory examination

1. **Chest radiographic** findings depend on the surgical history. The presence of a right aortic arch may be confirmed. A concave deficiency of the left heart border reflects various degrees of pulmonary arterial hypoplasia. Upturning of the apex from RVH causes the classic finding of a “boot-shaped” heart. Pulmonary vascular markings may vary throughout the lung fields, depending on associated branch pulmonary artery stenosis and relative blood flow. Calcification or aneurysmal dilation of surgical conduits or RV outflow tract repair may be visible on plain radiographs.
2. An **electrocardiogram** usually demonstrates sinus rhythm with RVH. Both atrial and ventricular rhythm disturbances can be present. The QRS axis is usually normal or rightward. If left axis deviation is present, an associated AV canal defect should be suspected. A patient who has undergone surgical repair typically has right bundle branch block. **A QRS duration of > 180 milliseconds is a predictor of sustained ventricular tachycardia and sudden cardiac death.**

D. Diagnostic testing

1. Echocardiography

- a. For a child or young adult, transthoracic echocardiography may be the only modality necessary for diagnosis. For adults or patients who have undergone surgical intervention, catheterization or magnetic resonance imaging (MRI) may be necessary in order to identify the presence and location of residual lesions.

- (1) Adequate views are obtained of the right heart, RV outflow tract, and proximal pulmonary arteries. Helpful views to identify a residual VSD or the presence of aortic insufficiency include the parasternal long-axis, parasternal short-axis, and apical four-chamber views. Further definition of residual lesions in the branch pulmonary arteries may be possible with a high parasternal short-axis view.
- (2) Palliative shunts are often best visualized in the suprasternal notch view where the subclavian arteries course distally.
- (3) Continuous flow is typically demonstrated with color Doppler techniques. Less common shunts may be difficult to image in adult patients. Aortopulmonary collateral vessels are extremely difficult to visualize, but may be seen in suprasternal notch views of the descending aorta.

- b. **Transesophageal echocardiography** may allow improved imaging of the intracardiac anatomic structures in adults, but limitations often remain with regard to the distal pulmonary arteries, and additional testing is frequently necessary.

2. **Cardiac magnetic resonance (CMR) imaging** is considered the gold standard for evaluating the right ventricle and quantitating pulmonary insufficiency in these patients. It can demonstrate the presence of scar, distal pulmonary arterial anatomy, and RV aneurysms, as well as other associated defects. It can also provide hemodynamic information about residual lesions. Previously placed shunts and possibly aortopulmonary collateral vessels can be identified as well. The anatomic information may be sufficient to proceed with surgical treatment or to guide the interventional cardiologist in planning a transcatheter procedure.

3. **Cardiopulmonary testing** should be performed as a baseline study and with progression of symptoms. It is useful in determining the timing for reintervention in the setting of RV volume overload secondary to free pulmonary insufficiency.

4. **Quantitative pulmonary flow scans** are useful to determine discrepancies in pulmonary flow that may be caused by branch pulmonary artery stenosis. These scans also provide objective baseline clinical information when obtained after surgical or transcatheter intervention.

5. The role of **cardiac catheterization** is decreasing with the advent of other imaging modalities, but can be helpful in assessing residual shunts and pulmonary hypertension.

- a. **Right heart catheterization.** Residual shunts are actively sought at the atrial and ventricular levels. The pulmonary arteries and branches are evaluated extensively in search of peripheral pulmonary stenosis. Findings at right heart catheterization and their clinical significance are as follows:

- (1) RV pressure is generally systemic in a patient who has not undergone surgical repair.
- (2) After surgical repair, elevated RV pressure suggests the presence of residual obstructive lesions, the levels of which are to be documented.
- (3) Careful pullback recordings are performed from the branch pulmonary arteries to the right ventricle because stenosis at each level is possible.
- (4) The presence of stenosis at a prior shunt site is expected.
- (5) RV end-diastolic pressures may be elevated in the setting of pulmonary insufficiency.

- b. **Left heart catheterization** is performed if noninvasive studies suggest residual VSD.
 - (1) **Angiography** includes a cranialized right ventriculography and possibly selective pulmonary arterial injections if hemodynamic findings suggest stenosis.
 - (2) **Left ventriculography** better demonstrates residual VSD in the presence of subsystemic RV pressures.
 - (3) **Aortic root injection** demonstrates the presence of aortic insufficiency, confirms the presence of grossly abnormal coronary artery origins or branching patterns, and reveals prior surgical shunts or aortopulmonary collateral vessels. If present, shunts and collateral vessels are best visualized in the posteroanterior and lateral projections after selective injection by hand.
 - (4) **Selective coronary angiography** is recommended in the care of adult patients to exclude acquired coronary artery disease and to identify the path of any anomalous coronaries before surgical intervention. **The anomaly that is not to be missed is the left anterior descending artery originating from the right coronary artery**—it crosses the RV outflow tract anteriorly and can be damaged during surgery.
- E. Therapy and follow-up care**
1. **Medical treatment**
 - a. If an adult has **not been surgically treated or has undergone palliative treatment**, a relatively well-balanced situation must exist. However, the following problems are to be expected.
 - (1) Long-term effects of RV outflow obstruction
 - (2) Progressive infundibular pulmonary stenosis
 - (3) Exposure of the pulmonary circulation to systemic shunt flow
 - (4) Development of distal pulmonary arterial stenosis, typically at shunt sites
 - (5) Erythrocytosis
 - (6) Chronic hypoxemia
 - (7) Pulmonary hypertension
 - (8) Paradoxical emboli
 - (9) Atrial and ventricular arrhythmias
 - (10) Increased risk of aortic insufficiency over time
 - (11) Endocarditis
 - b. Follow-up care increasingly involves **patients who have undergone surgical repair** and management of residual postoperative lesions.
 - (1) These patients are at increased risk for **sudden cardiac death**. Atrial and ventricular rhythm disturbances are common in the postoperative patient. Frequent Holter monitoring is warranted for this reason. Atrial tachyarrhythmias are found in up to one-third of patients and are predictive of morbidity and mortality. If patients are found to have nonsustained ventricular tachycardia, an electrophysiologic study and possibly an implantable cardioverter-defibrillator implantation can be considered. Atrial and ventricular arrhythmias may be the presenting problem for post-repair patients when a component of the repair is failing. There are no data to support prophylactic antiarrhythmic therapy to lower risk of sudden death in this patient population. An increased incidence of ventricular rhythm abnormalities has been associated with RV volume overload from pulmonary insufficiency and with QRS prolongation > 180 milliseconds (QRS duration correlates with degree of RV dilation).
 - (2) **Pulmonary insufficiency** can be tolerated for years, even decades, but chronic volume loading of the right ventricle can lead to diminished exercise tolerance, dysrhythmias, and **right heart failure**. Pulmonary

insufficiency is the most common indication for redo surgery after an initial repair.

- (3) Residual VSD
- (4) Progressive dilation of the ascending aorta
- (5) Residual RV outflow tract gradient
- (6) RV outflow tract aneurysm at previous patch site
- c. Recent **infective endocarditis guidelines** have departed considerably from prior iterations such that antibiotic prophylaxis is recommended only for those who are at highest risk for adverse outcomes from endocarditis. Specifically, prophylaxis is still appropriate for patients with TOF who are unrepaired, including those who have undergone a palliative procedure. For patients with TOF who have undergone total repair, antibiotic prophylaxis is now recommended only for 6 months following the placement of prosthetic material or device or if there is a residual defect at, or adjacent to, the site of prosthetic material (VSD patch leak, for example). If the pulmonary valve has been replaced or repaired with prosthetic material, antibiotic prophylaxis is appropriate as well.
2. The primary therapeutic consideration for patients with TOF is **surgical intervention**—either repair or reintervention.
 - a. The goal of **total repair** is to relieve the outflow tract obstruction while maintaining competency of a preferably native pulmonary valve with closure of the VSD. Some younger patients need extensive reconstruction of the RV outflow tract with early placement of a bioprosthetic valved conduit or homograft. In time, these usually become restrictive to flow and/or are insufficient. The result is progressive right heart hypertrophy, fibrosis, and failure if revision is not performed.
 - b. A common indication for **reintervention** is pulmonary valve replacement (PVR) for severe pulmonary valve insufficiency. The ideal timing for PVR, however, remains controversial. Cardiac MRI may be helpful in determining optimal timing, and there is evidence to support pursuing pulmonic valve replacement before the RV end-diastolic volume index reaches 160 mL/m².
 - c. Other indications for **reintervention** include the replacement or revision of conduits/homografts in the presence of symptoms, residual VSD with reasonable shunt (approximately 1.5:1), RV pressures greater than two-thirds of systemic pressures because of residual obstructive lesions, progressive aneurysmal dilation of RV outflow tract patch, residual systemic–pulmonary shunts with left ventricular volume overload, clinically significant arrhythmias, symptomatic or progressive aortic insufficiency, and dilated aortic root > 5.0 cm.
3. Although the mainstay of therapy has been surgical, **transcatheter techniques** are increasingly used to treat patients in certain situations. For the most part, transcatheter therapies for adults with TOF are limited to patients who have undergone prior surgical treatment, with attention to residual obstructive lesions in the main pulmonary artery, right ventricle–to–pulmonary artery conduit, or distal pulmonary arteries. Prior shunt sites may become stenotic with time and necessitate balloon angioplasty and possibly stent placement. Residual VSD and ASD may be closed percutaneously in select situations. Percutaneous pulmonic valve replacement has been approved for use both in Europe and the United States. The Melody valve (Medtronic; Minneapolis, MN) is a therapeutic option available for selected patients with stenotic or regurgitant conduits 23 mm or less in size.

II. COMPLETE TRANSPOSITION OF THE GREAT ARTERIES (pTGA). This is a relatively common congenital anomaly that occurs with a prevalence of 20 to 30 in 100,000 live births and is found more often in males (2:1). It is not associated with other syndromes and does not tend to cluster in families. Although it represents **5% to 8% of**

all congenital heart disease, it accounts for **25% of deaths in the first year of life**. Adult patients almost invariably have undergone prior surgery and carry with them important morbidities that require ongoing surveillance and care.

A. Anatomy

1. The defining feature of this anomaly is **ventriculoarterial discordance**, in which there is an abnormal alignment between the ventricles and great arteries. Hence the aorta arises from the right ventricle and the pulmonary artery arises from the left ventricle, creating two parallel circuits instead of one in series. Deoxygenated blood flows from the right atrium across a tricuspid valve → right ventricle → aorta, whereas oxygenated blood flows from the left atrium across the mitral valve → left ventricle → pulmonary artery. Unless there is bidirectional shunting at the atrial (ASD), ventricular (VSD), or great artery level (patent ductus arteriosus) to allow mixing of blood, this anatomy is incompatible with life (Fig. 32.1).
2. There is an abnormal spatial relationship between the great arteries such that instead of the normal spiral configuration, they run parallel to one another. The **aorta is rightward and anteriorly displaced**, whereas **the pulmonary artery occupies a position more leftward and posterior**. This is the most common pattern, but other configurations can also be seen such as side-by-side great arteries with the aorta to the right or an aorta directly anterior to the pulmonary artery.
3. Associated cardiac anomalies include **VSD in 40%** to 45% of cases (usually perimembranous but can involve any portion of the interventricular septum), **left ventricular (or subpulmonary) outflow tract obstruction in 25%**, aortic coarctation in 5%, patent foramen ovale (PFO), and patent ductus arteriosus. Patients with these associated cardiac anomalies are considered to have **complex** transposition, whereas patients without these associated anomalies are considered to have simple transposition.
4. This lesion is also referred to as “dTGA,” in which the “d” refers to the dextroposition of the bulboventricular loop, which is characterized by a right-sided right ventricle.
5. The coronary anatomy in dTGA is variable. The aortic sinuses are described according to their relationship to the pulmonary artery, such that the “facing

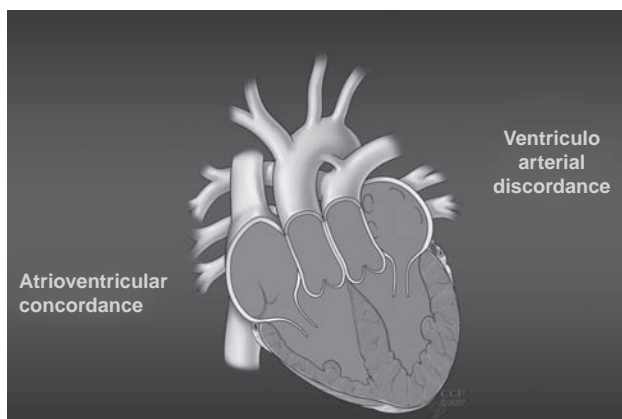


FIGURE 32.1 Complete (d) transposition of the great arteries.

sinuses” are closest to the pulmonary artery. The most frequent coronary arrangement is when the “left-facing” sinus gives rise to the left main coronary artery, whereas the “right-facing” sinus gives rise to the right coronary artery.

B. Natural history and surgical repair

1. Without surgical intervention, survival beyond infancy is dismal, with 89% mortality by the first year of life and worse outcomes for those without an associated lesion to allow for adequate mixing of blood. At birth, infants are treated with intravenous prostaglandin E to keep the ductus arteriosus open and some may undergo a **Rashkind procedure** (refer Table 32.1) to improve oxygenation until definitive surgery can be performed.
2. Adults invariably have undergone some type of cardiac surgery, although in rare cases they may present with Eisenmenger physiology (see subsequent text) if a “balanced” situation exists with a concomitant large VSD and pulmonary vascular disease. Surgical repairs include the atrial switch procedure (**Senning or Mustard operation**), the **arterial switch** procedure (Fig. 32.2), or the **Rastelli operation** (Table 32.1).

C. Clinical presentation

1. The clinical presentation of the surgically repaired patient with dTGA depends on the type of previous surgery. Although no longer cyanotic, these patients have a host of mid- to late-term morbidities that require lifelong surveillance. Patients who have undergone an arterial switch procedure are approaching adulthood only now and presenting in adult congenital cardiology clinics.
2. **Atrial switch**
 - a. Patients who have undergone an atrial switch operation often report New York Heart Association (NYHA) functional class I–II symptoms, but on exercise testing may have significant exercise intolerance. They have a systemic right ventricle, which, over time, can develop systolic dysfunction and progressive tricuspid regurgitation. These patients may present with signs and symptoms of congestive heart failure—the most common cause of death. Arrhythmias are common and patients may present with palpitations,

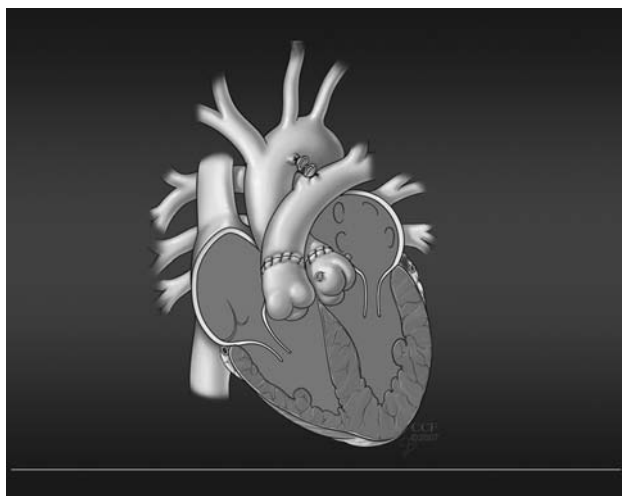


FIGURE 32.2 Arterial switch operation.

presyncope, or syncope. Venous baffle obstruction can lead to peripheral edema, hepatomegaly, ascites, and fatigue due to low cardiac output. The obstruction of the superior limb can produce a superior vena cava syndrome. Pulmonary venous baffle obstruction can lead to fatigue, exertional dyspnea, and chronic cough. Baffle leaks are often asymptomatic, but large leaks can lead to intracardiac shunting and cyanosis.

- b. On physical examination, focus should be on signs of AV regurgitation and heart failure. There may be an RV heave at the left sternal border on palpation. S_2 is loud at the second left intercostal space from an anterior aorta. Audible splitting of the S_2 may indicate the development of pulmonary hypertension.
- 3. **Arterial switch**
 - a. The majority of these patients are asymptomatic with NYHA functional class I symptoms. Arrhythmias are not a significant problem with this subset. Few will present with chest pain, and in these patients ischemia must be ruled out.
 - b. The physical examination is sometimes notable for turbulence across the RV outflow tract, which may be palpated as a thrill. The diastolic murmur of aortic insufficiency should also be sought.
- 4. **Rastelli operation**
 - a. Both atrial and ventricular arrhythmias are mid- to late-term complications, and these patients may present with palpitations or syncope. Conduit obstruction may manifest as insidious exercise intolerance, dyspnea, or new-onset arrhythmias. On physical examination, the character of the pulmonary ejection murmur should be carefully noted to evaluate for conduit obstruction.

D. Laboratory examination

- 1. The **chest radiograph** of patients with dTGA displays a narrow mediastinum due to the parallel orientation of the great arteries. The cardiothoracic silhouette is normal. The pulmonary vasculature is normal in patients without pulmonary hypertension. The right ventricle-to-pulmonary artery conduit in patients who have undergone a Rastelli procedure may be visualized on plain radiograph due to calcification.
- 2. In patients who have undergone an atrial switch operation, the **electrocardiogram** may display an ectopic atrial or junctional rhythm due to loss of sinus node function. There is usually right-axis deviation and RVH as a result of the systemic position of the right ventricle. In patients who have undergone arterial switch, RVH is distinctly abnormal and suggests pulmonary outflow tract obstruction. After a Rastelli operation, the electrocardiogram is notable for a right bundle branch block and patients may develop complete heart block.

E. Diagnostic testing

- 1. **Transthoracic echocardiography** in atrial switch patients can assess the degree of tricuspid regurgitation and estimate RV function. Color Doppler is helpful in detecting baffle leaks or obstruction, although more detailed analysis may require transesophageal echocardiography. For those who have undergone arterial switch, transthoracic echocardiography can assess left ventricular function and help exclude supraventricular and pulmonary artery stenosis. Two-dimensional Doppler can be used to look for conduit stenosis after the Rastelli operation and estimate RV systolic pressures. It can also exclude any residual VSDs in these patients.
- 2. As in the TOF population, **CMR** imaging has emerged as an invaluable imaging modality for patients with repaired dTGA. For postatrial switch patients, CMR imaging is used to quantify the size and function of the right ventricle, assess tricuspid regurgitation, and evaluate the systemic and pulmonary venous limbs of the atrial baffle for potential obstruction or leaks. In patients who have undergone

arterial repair, right and left ventricular function can be quantitated and both the right and left outflow tracts examined. Focus is placed on the great arteries to look for the presence of supravalvular and branch pulmonary artery stenosis as well as dilation of the neo-aorta. Conduit stenosis and gradients as well as RV size and function can be determined in those who have had a Rastelli operation.

3. **Cardiopulmonary testing** is very useful in detecting subtle clinical changes and decrease in functional capacity. As mentioned previously, there is often a discrepancy between self-reported symptoms and performance on metabolic exercise testing. Patients who have undergone atrial switch often have chronotropic incompetence and may benefit from pacemaker implantation. Stress testing may be useful in patients after arterial switch to detect coronary artery stenosis and resultant ischemia.
4. **Quantitative pulmonary flow scans** are an important part of the diagnostic work-up for suspected pulmonary artery or branch pulmonary artery stenosis in those who have undergone arterial switch repair. It is useful to obtain these scans before and after potential intervention to assess for functional improvement.
5. **Cardiac catheterization** does not have a role in the routine management of these adult patients. It does have a role, however, in the diagnosis and treatment of baffle obstruction and leaks, pulmonary hypertension, pulmonary artery stenosis, coronary artery stenosis, conduit obstruction, and residual VSD.

F. Therapy and follow-up

1. Follow-up should focus on potential late complications after repair and depends on the type of surgery the patient has undergone.
 - a. Atrial switch
 - (1) Arrhythmias including sinus node dysfunction and intra-atrial reentry tachycardia (frequent Holter monitoring is recommended)
 - (2) RV dysfunction
 - (3) Tricuspid regurgitation
 - (4) Sudden cardiac death
 - (5) Baffle obstruction or leak
 - (6) Pulmonary hypertension
 - (7) Endocarditis
 - b. Arterial switch
 - (1) Supravalvular or peripheral pulmonary artery stenosis
 - (2) Pulmonary outflow tract obstruction
 - (3) Neo-aortic regurgitation and aortic root dilation
 - (4) Coronary artery stenosis leading to ischemia and sudden death
 - (5) Left ventricular dysfunction
 - (6) Endocarditis
 - c. **Rastelli operation**
 - (1) Atrial and ventricular arrhythmias
 - (2) Complete heart block
 - (3) Sudden cardiac death
 - (4) Left ventricular dysfunction
 - (5) Conduit stenosis
 - (6) Endocarditis
2. **Medical management**
 - a. In the treatment of systemic RV dysfunction, there are limited data to suggest any long-term benefits from applying the evidence-based drugs utilized for left ventricular dysfunction. Despite this, angiotensin-converting enzyme (ACE) inhibitors are often utilized for afterload reduction. β -Blockers should be used with caution in patients after atrial switch repairs, as this could precipitate heart block (due to sinus node and AV conduction abnormalities).
 - b. As mentioned previously, the latest **infective endocarditis** guidelines have changed such that in the absence of valve replacement or prosthetic material

used to repair a valve, implantation of prosthetic material within the last 6 months, or prosthetic material accompanied by residual leaks, it is no longer officially recommended that dTGA patients post-repair receive antibiotic prophylaxis.

3. Late intervention options include both surgical and transcatheter procedures and, again, depend on the type of repair. Systemic ventricular failure may ultimately require work-up for orthotopic heart transplantation.

a. Atrial switch

- (1) The procedure of choice in patients with baffle obstruction is transcatheter stent implantation, with best results in the systemic venous baffle. Although technically more challenging, transcatheter dilation of the pulmonary venous baffle can be performed but may require surgical revision. Clinically significant baffle leaks can be treated with catheter-based techniques as well as with septal occluder devices.
- (2) Due to the high prevalence of atrial arrhythmias and sinus node dysfunction, these patients are referred for radiofrequency ablation procedures and pacemaker implantation.
- (3) Conversion to an arterial switch for systemic RV dysfunction or left ventricular “training” by pulmonary artery banding has not been reliably successful in the adult population and has been largely supplanted by cardiac transplantation in many centers.

b. Arterial switch

- (1) Percutaneous balloon angioplasty with or without stent placement is an excellent option for those with pulmonary artery and supra-aortic or branch pulmonary artery stenosis with suitable anatomy. Balloon angioplasty being a safe procedure, there is an approximately 15% restenosis rate, with lower risk after stent implantation. The greatest success lies with branch pulmonary artery stenosis.
- (2) Coronary artery stenosis can be treated with both stenting and coronary bypass surgery.
- (3) Severe neo-aortic regurgitation is treated surgically with either valve repair or replacement.

c. Rastelli operation

- (1) All right ventricle to pulmonary artery conduits inevitably fail and require replacement. There is a role for percutaneous stenting of conduit obstruction in some patients, as this can delay the need for surgery. These transcatheter procedures have a risk of stent fracture as well as potential for coronary artery compression, which can lead to catastrophic outcomes in the catheterization laboratory.
- (2) Residual VSD leaks may be amenable to closure by percutaneous means, but often require surgical revision. Clinically significant residual left ventricular outflow tract obstruction is also managed surgically.

III. CONGENITALLY CORRECTED TRANSPOSITION OF THE GREAT ARTERIES (ccTGA).

Ventricular inversion or ccTGA is a rare congenital anomaly that occurs in < 1% of children with congenital cardiovascular defects. Among these patients, it is equally rare to have no other associated structural abnormalities. The natural history of ccTGA is gradual congestive failure caused by systemic AV valve insufficiency and systemic ventricular dysfunction, even in the absence of other associated malformations. The presence of associated defects and conduction abnormalities contributes to a further decrease in life expectancy without intervention. Life expectancy is generally good but does not reach normal.

A. Anatomy

1. The defining feature of this congenital abnormality of cardiac looping is **AV and ventriculoarterial discordance**. Blood flows from the right atrium across

a mitral valve → right-sided, morphologic left ventricle → pulmonary artery → lungs → left atrium across a tricuspid valve → left-sided, morphologic right ventricle → aorta (Fig. 32.3).

2. The great arteries are not in their normal configuration and often run parallel to one another instead of crossing. The pulmonary artery is more posterior and rightward than usual and the aorta is more anterior and leftward.
3. The anatomic coronary arteries, like the AV valves, follow their respective ventricles. The left-sided coronary artery resembles the anatomic right coronary artery as it courses in the AV groove and gives rise to infundibular and marginal branches. The right-sided coronary artery resembles the morphologic left coronary artery, which branches into the anterior descending and circumflex arteries (Fig. 32.4).
4. The conduction system likewise follows the respective ventricle, as the right-sided, morphologic left ventricle depolarizes first. Accessory AV nodal tissue is located anteriorly with respect to normal, and the His bundle must traverse

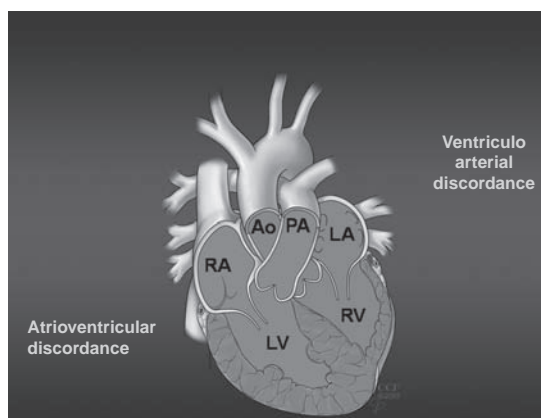


FIGURE 32.3 Congenitally corrected (l) transposition of the great arteries. Ao, aorta; LA, left atrium; LV, left ventricle; PA, pulmonary artery; RA, right atrium; RV, right ventricle.

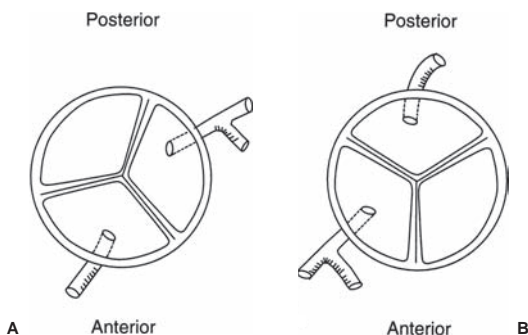


FIGURE 32.4 Schematic representation of coronary artery origins and branching in the normal heart (A) and in a congenitally corrected transposition (B).

anterior to the pulmonary artery and along the superior margin of a VSD if present. There is increased risk of acquired **complete heart block** in this lesion because of the abnormally placed AV node and its extended course. Approximately 30% of adolescents and adults develop complete heart block, the incidence of which is 2% per year without surgical intervention, with the site of block being within or above the His bundle. Accessory pathways have been described and are typically left-sided in the presence of an Ebstein anomaly–like malformation of the left-sided (tricuspid) AV valve.

5. Isolated ccTGA is the exception. **Associated lesions** are common and are considered in the diagnostic evaluation. They include VSD (70%), pulmonary outflow obstruction (~40% and usually subvalvular), or abnormalities of the left-sided, systemic tricuspid valve. Up to 90% of patients have an abnormality of the tricuspid valve in some form (i.e., dysplastic or Ebstein-like tricuspid valves).

B. Clinical presentation

1. Because physiologic blood flow is preserved, patients may have no symptoms through adulthood in the absence of other structural lesions or associated complications. This scenario is rare, however, because associated lesions commonly dictate the clinical features.
2. Without associated structural abnormalities, **failure of the systemic morphologic right ventricle** with various degrees of systemic AV valve (tricuspid) insufficiency is the norm. In this setting, the patient has nonspecific descriptions of fatigue, shortness of breath, and exercise intolerance or congestive failure. Patients may have **syncope or presyncope** caused by conduction abnormalities or complete heart block.
3. On physical examination, there is a loud A_2 due to an anterior and leftward aorta. The murmurs of a VSD or pulmonary stenosis may also be appreciated. Tricuspid insufficiency can be heard with systemic ventricular failure.

C. Laboratory examination

1. In the usual anatomic configuration of ccTGA, the aorta is anterior and to the left, which produces a **chest radiograph** with a straight left heart border. The left pulmonary artery is not well defined and the ascending aorta is not visible on the right. The chest radiograph may appear normal or reflect the presence of associated lesions, such as increased pulmonary flow from a VSD or decreased pulmonary flow in the setting of pulmonary stenosis. Dextrocardia occurs in approximately 20% of these patients and the diagnosis should be suspected if seen with abdominal situs solitus.
2. The typical **electrocardiogram** shows a left axis deviation. Among pediatric patients, there is loss of the usual Q waves in the precordial leads, with deep Q waves in leads II and aVF reflecting reverse septal activation. A variety of AV node conduction abnormalities may manifest with time and progress to complete heart block.

D. Diagnostic evaluation

1. In most instances, the diagnosis can be made with **echocardiography**. The essential findings of AV and ventriculoarterial discordance must be demonstrated. Imaging may be difficult in the presence of dextrocardia or mesocardia. Close attention must be paid to the morphologic details of each chamber.
 - a. The morphologic **right ventricle** is identified on the basis of its **triangular** shape, the presence of **trabeculations and moderator band**, an inferiorly positioned AV valve, and the absence of AV valve attachments to the interventricular septum.
 - b. The morphologic **left ventricle** is identified on the basis of its bullet shape, smooth wall, and more superiorly positioned AV valve and presence of AV valve attachments to the interventricular septum. In the case of ccTGA, these relationships are preserved but reversed.

- c. There is lack of anatomic continuity between the **left-sided (tricuspid) AV valve and aorta**, but continuity is present between the **right-sided (anatomic mitral) valve and pulmonary artery**. The left-sided AV valve is displaced inferiorly relative to the right-sided (mitral) valve and may appear malformed or have the characteristics of Ebstein anomaly.
 - d. Apical four-chamber and subcostal images are particularly helpful. The suprasternal notch view is essential in evaluating the great vessels that lie parallel to each other.
 - e. The **aortic arch** typically lies to the left of midline in the sagittal plane and can often be visualized from the high left parasternal position. Because variations in great vessel position occur, the spatial orientation must be clarified.
 - f. **Associated defects** (e.g., systemic AV valve insufficiency, VSD, and outflow tract obstruction) with ccTGA must be excluded or defined.
2. **Catheterization is unnecessary** for the diagnosis of ccTGA, but may be helpful in preoperative planning with regard to the hemodynamic significance of associated lesions. In rare instances, ccTGA is diagnosed by catheterization and was not recognized during routine echocardiography. An unusual arterial catheter course is caused by the anterior and leftward position of the aorta in most instances. The left-sided coronary artery typically arises from the posterior sinus and assumes a right coronary branching distribution, whereas the right-sided coronary artery arises from the anterior and rightward sinus and assumes a typical left coronary branching distribution (Fig. 32.4). Because the ventricular septum often lies in the sagittal plane, ventriculography is usually best performed in the straight posteroanterior and lateral projections.

E. Therapy

1. **Medical management** is dictated primarily by the associated malformations.
- a. In the rare case of isolated ccTGA, the risk of development of conduction abnormalities is cumulative over time; therefore, periodic Holter monitoring is warranted. Permanent pacemaker placement is often needed.
 - b. The systemic AV valve and ventricle may show signs of failure that necessitate initiation of heart failure measures in the form of diuretics and afterload reduction, although data are lacking for the use of agents such as ACE inhibitors or β -blockers in systemic right ventricles.
 - c. Associated lesions such as pulmonary stenosis or atresia, severe systemic AV valve regurgitation, or VSD may likewise contribute to the medical treatment of these patients, but often also necessitate surgical intervention.
 - d. The recent American Heart Association (AHA) guidelines do not recommend routine antibiotic prophylaxis for these patients unless they have had recent placement of prosthetic material within the preceding 6 months or have a leak at, or adjacent to, the site of a previous prosthesis.
2. **Surgery**
- a. Infants and children who are brought to medical attention early often need surgical intervention in the form of relief of pulmonary outflow tract obstruction or placement of palliative shunts, depending on the associated lesions.
 - b. For selected children, a **double switch** procedure may be performed. An **atrial switch** corrects the AV discordance by baffling atrial blood to the appropriate ventricle (i.e., oxygenated blood diverted from the left atrium rightward to the right-sided left ventricle and vice versa by the Mustard or Senning procedure). **Arterial switch** is performed in the same operation to restore anatomic ventriculoarterial concordance. The double switch operation may necessitate a period of “training” of the left ventricle by means of pulmonary artery banding. The results of this operation are generally less favorable in older patients in whom the right ventricle has been the systemic ventricle for a more prolonged period. The intermediate-term results of this procedure are encouraging, but data for long-term results are limited. Those

with a large VSD may undergo atrial baffling with a **Rastelli operation** (see Table 32.1).

- c. Adult patients with symptoms of progressive systemic AV valvular insufficiency may need valve repair or replacement. Most centers that have reported results with this procedure have found improved functional status after surgical treatment and acceptable risks. The timing of surgical intervention among patients with less severe symptoms is a topic of debate, but it is agreed that referral should be considered early before irreversible changes in ventricular function occur.

IV. EBSTEIN ANOMALY. This anomaly of the tricuspid valve represents 0.5% of congenital heart defects. The natural history of this lesion varies from early death to nearly normal expected survival, depending on the degree of tricuspid valve involvement and the presence and type of arrhythmias. An increased risk of **sudden death** irrespective of functional class, presumably caused by arrhythmia, has been observed. **Predictors of poor outcome** include earlier **age** at presentation, **cardiomegaly**, severe **RV outflow abnormalities**, and **disproportionate dilation of the right atrium** relative to the other chambers. There is an association with maternal lithium administration, but most cases are sporadic.

A. Anatomy

1. The **tricuspid valve** is morphologically and functionally abnormal. The basic features include adherence of the septal and posterior leaflet to the myocardium, which lowers the functional annulus toward the RV apex. This results in the classic **atrialization** of the right ventricle (Fig. 32.5) and dilation of the true tricuspid annulus. The anterior leaflet usually is not displaced, but is redundant and may be fenestrated and tethered.
2. **Associated structural anomalies** include a **PFO or ASD** (found in $\geq 80\%$), **VSD, mitral valve prolapse, and pulmonary stenosis**. ccTGA is associated with Ebstein-like anomaly of the tricuspid (systemic) valve.

B. Clinical presentation

1. **Signs and symptoms** are variable.
 - a. The presence of a severely insufficient valve can be apparent at birth because of right-to-left shunting across a stretched PFO or ASD, resulting in cyanosis. Pulmonary vascular resistance is high in the neonate and worsens cyanosis,

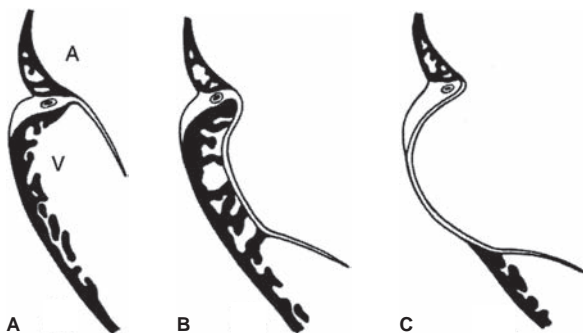


FIGURE 32.5 Section through the right atrioventricular junction. **A:** Normal heart, showing the right atrium (A) and right ventricle (V). **B:** Mild degree of Ebstein anomaly. **C:** Severe Ebstein anomaly. In **(B)** and **(C)**, there is apparent displacement of the tricuspid valve. (From Adams FH, Emmanouilides GC, Riemenschneider TA, eds. *Moss' Heart Disease in Infants, Children, and Adolescents*. 4th ed. Baltimore, MD: Williams & Wilkins, 1989, with permission.)

but as pulmonary vascular resistance falls, cyanosis may resolve. In adulthood, as tricuspid regurgitation becomes longstanding with associated decreased RV compliance, cyanosis can reappear. In subtle cases, the anomaly may not be evident until adulthood and then results in nonspecific fatigue, shortness of breath, palpitations, near-syncope, or syncope. In the presence of an interatrial communication, patients may present with paradoxical embolization or brain abscess. Because the spectrum of involvement varies greatly, a high index of suspicion must be maintained.

- b. The downward displaced septal leaflet creates a substrate for **accessory pathways**, and clinical Wolff-Parkinson-White syndrome is found in 10% to 25% of patients. Arrhythmias include supraventricular tachycardia mediated by an accessory pathway or caused by atrial arrhythmias from progressive atrial dilation. The combination of atrial fibrillation or flutter conducted rapidly across an accessory pathway is often poorly tolerated.

2. Physical examination

- a. General inspection usually reveals normal jugular venous pulsations despite severe tricuspid regurgitation, which is masked by a large compliant atrium. Cyanosis may be present as a result of right-to-left shunting at the atrial level. Digital clubbing will vary depending on the amount of cyanosis.
- b. The most common auscultatory findings are the regurgitant murmur of tricuspid insufficiency, gallop rhythms, multiple systolic ejection sounds, and a widely split S_2 .

C. Laboratory examination

- 1. **Chest radiography** may reveal cardiomegaly, caused by right atrial enlargement from tricuspid insufficiency. Typically, it is described as a globe-shaped heart with a narrow waist.
- 2. The **electrocardiogram** can demonstrate PR prolongation, right atrial enlargement ("Himalayan" P waves), and superior axis with or without right bundle branch block (Fig. 32.6). The QRS amplitude is characteristically low over the right precordial leads due to a diminutive right ventricle. The preexcitation pattern, if present, is almost always type B (i.e., left bundle branch pattern). Deep Q waves may be seen in leads II, III, and aVF from fibrotic thinning of the RV free wall and/or septal fibrosis.

D. Diagnostic evaluation

- 1. The diagnosis can be confirmed with transthoracic or transesophageal **echocardiography**, with the tricuspid valve readily visualized in the parasternal short-axis, apical four-chamber, and subcostal views.

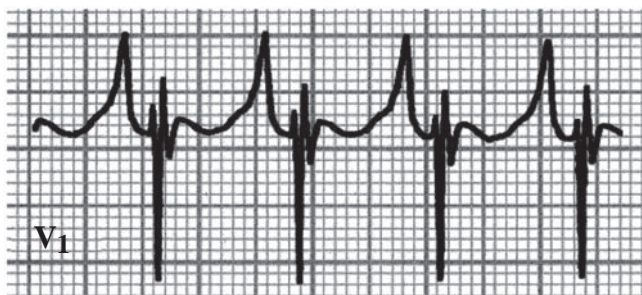


FIGURE 32.6 Lead V₁ of an electrocardiogram from a newborn infant with Ebstein anomaly demonstrates marked right atrial enlargement and an rSR' pattern.

- a. **Apical displacement of the septal leaflet** from the insertion of the anterior mitral valve leaflet by at least 8 mm/m² body surface area is considered diagnostic. In less obvious cases, only tethering of the septal leaflet may be found, defined as at least three accessory attachments of the leaflet to the ventricular wall causing restricted motion. An imperforate valve may rarely occur.
 - b. The **anterior leaflet** may produce functional obstruction of the pulmonary outflow tract. The leaflet in this circumstance is often called “sail-like.” The pulmonary outflow is carefully studied to discern functional obstruction from such a leaflet rather than true anatomic atresia of pulmonary outflow.
 - c. Views of the **atrial septum** are included in all studies to assess the size of the ASD and degree of shunting, if present.
 - d. The size of the **right ventricle** and true tricuspid annulus is assessed because size guides the feasibility of surgical intervention.
 - e. The size and function of the **left ventricle** are assessed. The shape of the left ventricle may be unusual because of extreme leftward bowing of the ventricular septum. Left ventricular function can be affected, and abnormalities may affect long-term outcome.
 - f. **Associated lesions** must be excluded, such as ASD, RV outflow tract obstruction, patent ductus arteriosus, and, in rare instances, mitral valve abnormalities with associated insufficiency.
2. **Cardiac catheterization is unnecessary** for the diagnostic evaluation of Ebstein anomaly, except to exclude coronary artery disease in adult patients with risk factors for whom surgical intervention is planned. Increased risk of cardiac arrest during catheterization has been reported. A diagnostic right heart study may be indicated in the presence of associated hemodynamic abnormalities as part of preoperative planning.
 3. Formal **electrophysiologic study** may be considered for patients with arrhythmias or for those being considered for surgical treatment. Radiofrequency ablation of accessory pathways is performed.
- E. Therapy**
1. A large number of adult patients may undergo **medical treatment**, which includes standard heart failure medications such as diuretics and digoxin. There are no good data to support ACE inhibitors in right heart failure due to Ebstein anomaly. Particular attention must be focused on the management of atrial dysrhythmias, which become more common with age. Permanent pacemaker therapy is required in 3.7% of patients, mostly for AV block and rarely for sinus node dysfunction. Endocarditis prophylaxis is no longer recommended for these patients unless they are cyanotic and unrepaired, have undergone placement of prosthetic material within the preceding 6 months (i.e., ASD occluder device), have a leak adjacent to or at the site of prosthetic material, or have had tricuspid valve replacement.
 2. **Surgical correction** usually is recommended for patients with NYHA functional class III–IV symptoms despite medical therapy. The tricuspid valve may be repaired primarily or complete replacement may be necessary, and an interatrial communication, if present, is closed. Patients with symptomatic cardiomegaly, cyanosis, or arrhythmias are considered for surgical intervention. Favorable results have been achieved at centers experienced in the care of adult patients, and functional class has improved after therapy.
 3. **Transcatheter closure** of an interatrial shunt can be considered in select patients with cyanosis at rest (oxygen saturation < 90%). Patient selection must be carefully evaluated, as closure of an ASD or PFO may lead to worsening RV dysfunction due to increased right-sided heart pressures. In the case of paradoxical embolic events (i.e., stroke), ASD/PFO closure is considered.

V. EISENMENGER SYNDROME. Eisenmenger syndrome is the clinical phenotype of an **extreme form of pulmonary arterial hypertension associated with congenital heart disease**. Over the last few decades, rapid advances in the modalities of diagnosis and treatment of congenital heart disease have resulted in the ability to repair defects at a much younger age. Pulmonary vascular injury is prevented in many of these children. However, Eisenmenger syndrome is still seen in older patients and occasionally in younger patients, particularly in those from developing countries where access to care may be limited. The natural history of Eisenmenger syndrome is variable; and although a cause of significant morbidity, many Eisenmenger patients survive 30 years or more after the onset of the syndrome.

A. Physiology. Patients with a systemic-to-pulmonary circulation connection will initially have left-to-right shunting of blood due to the lower pulmonary vascular resistance compared with systemic vascular resistance. Over time, because of excessive flow to the pulmonary vasculature resulting in increased shear and circumferential stress, pulmonary vascular resistance increases. Eventually, the shunt reverses, creating right-to-left flow. Although the classic form of the disease was initially used to describe the long-term consequences of a VSD, it can occur with any congenital defect with an initial left-to-right shunt including ASD, AV canal defect, patent ductus arteriosus, aortopulmonary window, and surgically created systemic-to-pulmonary artery shunts. It is important to note, however, that the **physiology and clinical presentation differ depending on the level of shunt**. In contrast to patients with nonrestrictive shunts at the ventricular or arterial level, most patients with ASDs do not develop Eisenmenger syndrome, and if they do, they present much later in life. In this case, atrial-level shunting is determined by the compliance of the ventricles and not due to systemic or supra-systemic pulmonary artery pressures.

B. Clinical presentation of Eisenmenger syndrome has multi-organ involvement

- 1. Symptoms.** Pulmonary congestion (from the left-to-right shunt) in early childhood may be evident from the history, but improves as the shunt reverses with ensuing cyanosis. Exercise intolerance is very common. Hypoxemia can lead to erythrocytosis and symptoms of hyperviscosity (e.g., headache, dizziness, fatigue, and cerebrovascular accidents). These patients can have a bleeding diathesis due to thrombocytopenia and inadequate clotting factors. This can complicate the management of intrapulmonary thrombosis, which occurs in up to one-third of patients. Hemoptysis is a common symptom—alone or due to pulmonary infarction. Infectious complications include bacterial endocarditis and septic cerebral emboli. Atrial arrhythmias and symptoms of congestive heart failure are usually a late sign and are associated with an increased risk of sudden cardiac death.
- 2. Physical examination.** The initial murmur of the associated lesion goes away with reversal of the shunt. Cyanosis and digital clubbing are present, and arterial pulses may be diminished. The cardiac examination reveals signs of elevated right heart pressure, such as jugular venous distention with a prominent *v* wave, a right parasternal heave, a loud pulmonary component of S_2 (sometimes palpable), a right-sided S_4 , a holosystolic murmur of tricuspid regurgitation, and a diastolic decrescendo murmur of pulmonary regurgitation. Signs of congestive heart failure such as peripheral edema, ascites, and hepatosplenomegaly are seen later in the disease course.

C. Laboratory examination

- 1. Chest radiography** is variable. It may show dilated, even calcified, central pulmonary arteries. Reduced peripheral lung markings are not commonly seen. Patients with ASDs tend to have cardiomegaly due to RV enlargement.
- The **electrocardiogram** shows evidence of right atrial enlargement and RV hypertrophy. The presence of atrial arrhythmias should be investigated, particularly in the presence of palpitations.

D. Diagnostic evaluation

1. **Echocardiography.** Two-dimensional echocardiography helps in the detailed assessment of the level of the defect, associated lesions, and ventricular function. Doppler measurements can demonstrate and assess the size of the shunt as well as RV pressure and volume overload.
2. **Cardiac catheterization.** Cardiac catheterization is often necessary in these patients to assess the pulmonary vascular resistance. Demonstration of pulmonary vasoreactivity to oxygen, nitric oxide, or other pulmonary vasodilators is prognostic for these patients and can help identify which patients will most benefit from advanced therapies for pulmonary arterial hypertension.

E. Therapy

1. Medical management

- a. Chronic nocturnal oxygen therapy has not been shown to be beneficial, although it may improve symptoms in some patients. Anticoagulation is controversial because it can also predispose to hemorrhage or hemoptysis, but it is helpful in preventing thromboembolic events. Hyperviscosity can be managed in *symptomatic* patients by performing phlebotomy with isovolumic replenishment, but **routine phlebotomy is contraindicated** due to its effect on iron stores, oxygen-carrying capacity, and increased risk of stroke. Monitoring of iron levels and iron replacement, therefore, is paramount. The management of right-sided heart failure is problematic and the use of digoxin in these patients is controversial. Diuretics should be used cautiously because aggressive diuresis predisposes to hyperviscosity and decreases preload. Endocarditis prophylaxis is warranted.
 - b. Over the last few years, there has been a paradigm shift regarding the treatment of pulmonary hypertension in Eisenmenger syndrome. While traditional therapy focused on preventive and palliative measures, there is accruing evidence to suggest that the **disease is in fact modifiable and that selective pulmonary vasodilators are not only safe but likely beneficial** in this population. These agents include endothelin antagonists, prostacyclin analogs, and phosphodiesterase-5 inhibitors. The only randomized, placebo-controlled trial performed to date in Eisenmenger patients, BREATHE-5, showed reduction in pulmonary vascular resistance and improvement in exercise capacity (with no detriment to oxygen saturation) using bosentan (an endothelin antagonist). In general, intravenous treatments are avoided in this population due to the risk of paradoxical embolism and increased infectious risk with indwelling lines.
2. **Surgical management.** Selected patients may be candidates for combined heart–lung transplantation or lung transplantation with concomitant repair of the intracardiac defect, if feasible. Timing of these interventions may be difficult because of the relatively long-term survival of these patients after the onset of the disease process and the recent availability of selective pulmonary vasoactive therapy.

F. Eisenmenger syndrome in special situations

1. **Travel** to areas of high altitude should be avoided because it may result in acute right heart failure. Air travel, however, is not contraindicated, as cabin pressures during commercial flights are generally well-tolerated.
2. **Pregnancy** in these patients is high risk to the fetus and the mother (> 50% maternal mortality) and is generally contraindicated. Given the high risk of maternal and fetal mortality, contraceptive methods (preferably without the use of estrogen) are critical. Elective termination should be discussed with pregnant Eisenmenger patients.
3. **Noncardiac surgery** is also associated with high risk and should be performed under the supervision of anesthesiologists familiar with Eisenmenger syndrome.

ACKNOWLEDGMENTS: *The authors thank Drs. Yuli Kim, Athar Qureshi, Keith Ellis, J. Donald Moore, and Douglas S. Moodie for their contributions to earlier editions of this chapter.*

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SECTION

VII

Clinical Cardiology

EDITOR

Brian P. Griffin

Syncope

I. INTRODUCTION

- A. Syncope is a common medical problem that accounts for approximately 6% of medical admissions and 3% of emergency room visits. Syncope is defined as a **sudden transient loss of consciousness with associated loss of postural tone. Recovery is spontaneous, without neurologic deficit and without requiring electrical or chemical cardioversion.** Generally, a fall in systolic blood pressure below 70 mm Hg or a mean arterial pressure of 40 mm Hg results in loss of consciousness. Cerebral blood flow usually decreases with aging, making the elderly at higher risk for syncope.
- B. Syncope as a symptom can be caused by a **variety of medical diseases that produce a transient interruption of cerebral blood flow.**
1. A genuine effort should be made to **determine a specific cause of syncope.** Identifying a specific cause can help in the selection of therapy, prevent recurrences, minimize expensive evaluations, and decrease morbidity.
 2. **Patients with cardiac syncope have higher rates of mortality and sudden death** at follow-up. Identifying and treating cardiac syncope can improve outcome.

- II. **CLINICAL PRESENTATION.** Although a variety of diagnostic tests are available for evaluation of syncope, a thorough history and physical examination are crucial to determine the cause and the best diagnostic approach. A good history and physical examination can provide a clue to the diagnosis in up to 50% of cases.

- A. **Signs and symptoms.** Accurately described symptoms can lead to specific diagnostic considerations, as illustrated in Tables 33.1 and 33.2. Table 33.3 lists the prevalence of various causes of syncope as seen in the Evaluation of Guidelines in Syncope Study 2 (EGSYS-2) trial, a prospective systemic evaluation of consecutive patients referred to various emergency rooms for syncope.
1. **The most important aspect of history taking is to determine the circumstances before syncope (i.e., the prodrome);** whether there is association with any particular activity, exertion, or change in position; and the frequency of occurrence.
 2. The initial approach to any patient with syncope should include a **search for the presence of structural heart disease such as valvular stenosis, cardiomyopathy, or myocardial infarction.** The presence of any of these may suggest more malignant causes such as ventricular tachycardia.
 3. **Symptoms of vasovagal syncope.** Calkins et al. (1) reported that a careful history could diagnose vasovagal syncope. They reported that **women (< 55 years) with a postsyncopal recovery period that included fatigue** and patients with **clear precipitating factors, diaphoresis, palpitations preceding syncope, and severe fatigue after syncope** were more likely to have vasovagal syncope than ventricular tachycardia or complete heart block.
 4. **Convulsive syncope.** Occasionally, a syncopal episode is accompanied by **mild muscular jerking** as a result of cerebral anoxia. This phenomenon is not true epilepsy, and the physician must make every effort to distinguish between

TABLE 33.1 Cardiovascular Causes of Syncope

Neurally mediated (vasovagal)
Situational
Micturition
Defecation
Postprandial
Swallowing
Coughing
Sneezing
Glossopharyngeal neuralgia
Orthostatic syncope
Carotid sinus syncope
Cardioinhibitory
Vasodepressor
Mixed
Mechanical
Aortic stenosis
Hypertrophic cardiomyopathy
Atrial myxoma
Mitral stenosis
Pulmonic stenosis
Pulmonary hypertension or embolism
Myocardial infarction
Cardiac tamponade
Electrical
Second- and third-degree atrioventricular block
Sick sinus syndrome
Supraventricular tachycardia
Ventricular tachycardia
Torsade de pointes
Pacemaker malfunction

syncope and a seizure. Syncope typically occurs without an aura and has a more deliberate onset. Seizures are characterized by severe jerking motions, longer periods of unconsciousness, and severe fatigue after the event (i.e., postictal state). Seizures may occur without regard to patient positioning. In contrast, syncope rarely happens when a person is recumbent.

- 5. Other entities that make diagnosis difficult are **vertigo, transient ischemic events, somatization disorders (e.g., conversion and hysteria), cataplexy, epilepsy, and drop attacks.**

TABLE 33.2 Clinical Features Suggesting Specific Causes

Symptoms or finding	Diagnostic consideration
After sudden unexpected pain, unpleasant sight, sound, or smell	Vasovagal syncope
During or immediately after micturition, cough, swallow, or defecation	Situational syncope
With neuralgia (glossopharyngeal or trigeminal)	Bradycardia or vasodepressor
Upon standing	Orthostatic hypotension
Taking hypotensive medication	Drug-induced syncope
Symptoms within 1 h after meals	Postprandial hypertension
Prolonged standing at attention	Vasovagal
Well-trained athlete after exertion	Vasovagal
Changing position (from sitting to lying, bending, turning over in bed)	Atrial myxoma, thrombus
Syncope with exertion	Aortic stenosis, pulmonary hypertension, mitral stenosis, HOCM, coronary artery disease
With head rotation, pressure on carotid sinus	Carotid sinus syncope
Associated with vertigo, dysarthria, diplopia	TIA, stroke
With arm exercise	Subclavian steal syndrome

HOCM, hypertrophic obstructive cardiomyopathy; TIA, transient ischemic attack.

Adapted from Kapoor WN, Smith M, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med.* 1994;97:78–88.

TABLE 33.3 Causes of Syncope in the Evaluation of Guidelines in Syncope Study 2 Trial

Neurally mediated	Orthostatic hypotension	Cardiac arrhythmia	Structural cardiopulmonary	Nonsyncopal
<ul style="list-style-type: none"> • Vasovagal • Carotid sinus • Situational <ul style="list-style-type: none"> • Cough • Micturition • Defecation • Swallow • Others 	<ul style="list-style-type: none"> • Drug induced • ANS failure <ul style="list-style-type: none"> • Primary • Secondary • Volume depletion 	<ul style="list-style-type: none"> • Brady <ul style="list-style-type: none"> • Sick sinus • AV block • Tachy <ul style="list-style-type: none"> • VT • SVT • Inherited 	<ul style="list-style-type: none"> • AMI • Aortic stenosis • HOCM • Pulmonary HTN • Others 	<ul style="list-style-type: none"> • Metabolic • Epilepsy • Intoxications • Drop attacks • Psychogenic • TIA • Falls
66%	10%	11%	5%	6%

Unknown cause: 2%.

AMI, acute myocardial infarction; ANS, autonomic nervous system; AV, atrioventricular; HOCM, hypertrophic obstructive cardiomyopathy; HTN, hypertension; VT, ventricular tachycardia.

Adapted from Brignole M. Diagnosis and treatment of syncope. *Heart.* 2007;93:130–136.

6. The examiner should always **carefully review the medications of a patient with syncope** for their potential role, directly or by interaction with other medications.

B. Physical findings

1. The **physical examination is especially important when the patient is unable to describe the event** and no witnesses are available, as certain findings on examination can direct the physician in the diagnostic evaluation.
2. The **comprehensive evaluation** should include a fundoscopic examination of the eye for evidence of embolism. The evaluation should also search for the presence of carotid bruit and assessment of the carotid upstroke; subtle neurologic deficits that may result from a stroke or neuropathy; cardiac murmurs with attention given to valvular findings and extra heart sounds (such as tumor plop); peripheral pulses for evidence of peripheral vascular disease and entities such as subclavian steal; and dermatologic clues that may suggest collagen vascular disease or vasculitis.
3. In examining a patient with syncope, it is important to check **blood pressure in both arms as well as orthostatic blood pressure**. Repeated orthostatic blood pressure measurements may be needed when there is a high level of clinical suspicion for orthostatic syncope (see Section II.C.1.c).
4. Syncope in the absence of underlying heart disease is not associated with increased mortality. The morbidity of such episodes is related to harm that may occur in association with a syncopal event.

C. Etiology and pathophysiology

1. **Neurally mediated syncope**. Vasovagal or neurally mediated syncope is the **most common cause of syncope**. Many situations can lead to vasovagal “fainting.” Examples include unpleasant smell, sudden pain, acute blood loss, and sustained upright posture. Vasovagal reactions are often preceded by an increase in heart rate and blood pressure.
 - a. **Neurocardiogenic syncope** is thought to be the result of **autonomic overactivity followed by a fall in peripheral vascular resistance, without a significant rise in cardiac output**. In susceptible individuals, the stimulation of mechanoreceptors located in the inferior and posterior wall of the left ventricle by stretch, cardiac distention, or rapid systolic contraction leads to increased neural discharges through unmyelinated C fibers to the vasomotor center in the medulla, resulting in enhanced parasympathetic and decreased sympathetic activities. The withdrawal of the sympathetic nervous system results in sudden bradycardia or hypotension. Animal studies suggest that cardiac afferents may not be required to initiate a vasodepressor response and that other potential mechanisms, such as release of endogenous opioids or nitric oxide inhibition of sympathetic nerve firing and primary central nervous system activation, may play a role in vasodepressor syncope.
 - b. **Situational syncope**. Patients often recall situational syncopal episodes. **Micturition, defecation, cough, and trumpet playing** are examples. The action causes a reflex vasodilation (vaguely mediated) that is exacerbated if the patient performs a Valsalva maneuver, which decreases the blood return to the right heart.
 - c. **Orthostatic syncope**. **Postural hypotension** is reported in up to 24% of elderly people. Normally when a person stands, the systolic blood pressure drops only 5 to 15 mm Hg, and the diastolic pressure rises slightly. In orthostasis, the decrease in systolic blood pressure exceeds 20 mm Hg; frequently, the diastolic pressure drops by > 10 mm Hg. This finding demands a search for a potential cause.
 - (1) Common causes include **volume depletion, medications, diabetes, alcohol, infection, and varicose veins**.

- (2) **Dysautonomic syndromes** causing orthostatic hypotension are divided into two categories: primary and secondary. Primary autonomic failure is idiopathic and includes pure autonomic failure (i.e., Bradbury-Eggleston syndrome) and multisystem atrophy (i.e., Shy-Drager syndrome). Secondary causes include amyloidosis, tabes dorsalis, multiple sclerosis, spinal tumors, and familial dysautonomia.
- a. **Carotid sinus syncope.** Less than 1% of patients presenting with syncope have been given a diagnosis of carotid sinus syncope. This entity should be considered in patients with spontaneous symptoms while shaving, swimming, turning the head, or wearing a tight collar, as well as in older patients with recurrent syncope. A cardioinhibitory response (i.e., bradycardia) occurs in about 70%, and a vasodepressor response (i.e., hypotension) occurs in 10%. The remaining patients have a mixed response (i.e., bradycardia with hypotension). Carotid sinus syncope is elicited by manual pressure on the carotid sinus and can be blocked by atropine. Clinical presentation along with findings of carotid sinus hypersensitivity in the absence of other potential causes is enough to make the diagnosis. Symptom reproduction during carotid massage is not necessary for a diagnosis. A positive carotid test result is defined by cardiac asystole of 3 seconds or longer, a drop in systolic blood pressure of > 50 mm Hg, or a drop of > 30 mm Hg in blood pressure and symptoms. Carotid massage should be avoided in patients with a history of stroke or transient ischemic attack (TIA) within 3 months (unless they have had normal carotid Doppler results) or those patients in whom carotid bruits are heard on clinical examination.
2. **Cardiac syncope**
- a. **Mechanical causes**
- (1) Syncope or related symptoms frequently occur with exertion and arise from left ventricular outflow obstruction, as seen in aortic stenosis or hypertrophic obstructive cardiomyopathy (HOCM). With exertion, peripheral vascular resistance falls, but the cardiac output is fixed, leading to hypotension. Arrhythmias and altered baroreceptor response also play a role in syncope in patients with an obvious mechanical cause, such as aortic stenosis.
 - (2) **Right ventricular outflow obstruction** can also result in syncope. This condition can also trigger a vasodepressor component by mechanisms similar to neurocardiogenic syncope.
 - (3) **Myocardial ischemia and infarction, pulmonary embolus, and cardiac tamponade** should be kept in mind. **Syncope may be the initial complaint in 7% of patients older than 65 years presenting with myocardial infarction.**
 - (4) **Patients with hypertrophic obstructive cardiomyopathy** have an annual risk of sudden death in nonselective populations of approximately 1% per year. Syncope increases the relative risk of sudden cardiac death by approximately fivefold. The presence or absence of other sudden death risk factors (family history of sudden cardiac death, nonsustained ventricular tachycardia, marked left ventricular hypertrophy, and significant left ventricular outflow tract gradient) influences the risk of sudden cardiac death. Electrophysiologic (EP) testing plays a minimal role in risk stratification, as does genotyping for specific mutations currently. Treatment in high-risk patients usually includes the use of β -blockers, calcium channel blockers, disopyramide and other antiarrhythmics, and frequently implantable cardioverter–defibrillator (ICD) placement.
 - (5) **Arrhythmogenic right ventricular dysplasia** is a disorder in which syncope is caused by ventricular tachycardia originating in the right ventricle secondary to replacement of myocardium by adipose tissue

and/or fibrosis. The imaging modality of choice is cardiac magnetic resonance imaging (usually with fat suppression), which usually shows thinning, aneurysms, and replacement of right ventricular myocardium with adipose and fibrotic tissues. It is thought to be a common cause of sudden cardiac death in patients younger than 35 years and may be familial in 30% to 50% of patients. It is usually diagnosed based upon the presenting electrocardiogram (ECG), suggested by the presence of premature ventricular contractions or sustained ventricular tachycardia with a left bundle branch morphology. Treatment of syncope in this setting usually includes ICD implantation, and yearly ICD appropriate therapy rates are usually 15% to 20%.

(6) Ion Channel disorders

(i) Long QT syndrome. This is characterized by prolongation of the QT interval, with a measured QTc > 450 milliseconds. The long QT syndromes are actually a heterogeneous group of disorders and have been mapped to genetic defects in either cardiac potassium channels (LQT1 and LQT2) or sodium channels (LQT3). It is worthwhile mentioning that the potassium channel mutations involve a loss of function of the potassium channels, whereas sodium channel mutations involve a partial gain of function. The lifetime risk of syncope or sudden cardiac death increases with increasing QTc, reaching 50% for QTc > 500 milliseconds. Syncope is usually the result of an episode of torsade de pointes or self-terminating polymorphic ventricular tachycardia and is an ominous finding. Treatment options include β -blockers and ICD implantation, as well as lifestyle modifications, including the restriction of strenuous or competitive exercise and avoidance of QT-prolonging drugs.

(ii) Brugada syndrome is a disorder of cardiac sodium channels that results in transient downsloping ST elevations in the anterior precordial leads and leads to a susceptibility to polymorphic ventricular tachycardia. Patients with Brugada syndrome with syncope have a 2-year risk of sudden cardiac death of approximately 30%; therefore, treatment with an implantable defibrillator is recommended.

b. Electrical causes. Ventricular tachycardia, sick sinus syndrome, and atrioventricular block are the most common causes of syncope related to arrhythmias. One must also consider supraventricular tachycardia, Wolff-Parkinson-White syndrome, and torsade de pointes. Arrhythmic syncope carries the worst prognosis and must be thoroughly evaluated.

(1) Primary cardiac arrhythmias are the most common cause of syncope in patients with known cardiac disease, such as previous myocardial infarction, left ventricular dysfunction, or cardiomyopathy.

(2) Medications that prolong the QT interval and electrolyte abnormalities should also be considered as causes of arrhythmic syncope.

(3) Patients with pacemakers should have their pacemaker interrogated for possible malfunction. The possible causes include battery depletion, lead malfunction, or lead dislodgment. Individuals with pacemaker or implantable defibrillators should be educated about the devices and examined regularly. An observed phenomenon in patients with atrial fibrillation who undergo atrioventricular nodal ablation (and are subsequently pacemaker dependent) is the development of syncope secondary to ventricular tachycardia, presumably because of an R on T phenomenon. Because of this, such patients are usually programmed with a higher backup rate (at least 90 beats per minute) for the 4 to 6 weeks following atrioventricular nodal ablation.

3. Noncardiovascular syncope

- a. **Neurologic causes** include stroke, TIAs, normal pressure hydrocephalus, and seizures. Other causes include orthostatic hypotension from dysautonomia, and this diagnosis should be suggested based on history, screening neurologic examination, and orthostatic vital signs.
 - b. **Metabolic causes** include arrhythmias induced by hypoglycemia, hypoxia, and hypokalemia.
 - c. **Psychogenic causes** include anxiety disorder, panic disorder, hyperventilation, somatization, depression, hysterical syncope (i.e., no change in blood pressure or pulse), and conversion disorder.
 - d. Drugs that can cause syncope include **nitrates, angiotensin-converting enzyme inhibitors, calcium channel blockers, β -blockers, quinidine, procainamide, disopyramide, flecainide, amiodarone, diuretics, vincristine, insulin, cocaine, and digoxin. The α -blockers** (e.g., prazosin) are potent agents and commonly cause orthostatic hypotension, especially in the elderly. These agents should be initiated with careful instructions to the patient regarding orthostasis and should be prescribed to be taken in the evening. Orthostatic hypotension can be induced by tricyclic antidepressants or antiparkinsonian agents as well.
4. **Unknown or unexplained causes.** Past studies indicated that 33% to 50% of patients with syncope had no identifiable cause. One study showed that these patients are still at a higher risk for subsequent death from any cause, with a multivariable-adjusted hazard ratio of death of 1.32 (95% confidence interval: 1.09 to 1.60). Other diagnostic tools such as tilt table testing, loop recorders, signal-averaged electrocardiography (SAECG), and EP studies may assist physicians in identifying a previously unknown cause of syncope.

Stress testing, electroencephalography, computed tomography of the head, and cerebral angiography have a very low yield unless there is a history of trauma, stroke, or seizures.

III. DIAGNOSTIC TESTING. A single ECG offers the possible diagnosis in approximately 5% of cases. It can demonstrate sinus pause, high-degree atrioventricular block, prolonged QT interval, or Wolff-Parkinson-White syndrome. Echocardiography, Holter monitoring, loop recorders, SAECG, EP testing, and tilt table testing are major diagnostic tools. Their yield depends on the presence or absence of underlying structural heart disease.

- A. In evaluating a patient with syncope, **it is important to differentiate patients with and without structural heart disease.** The goal of evaluation should be to obtain a correlation between symptoms and an abnormal finding during diagnostic testing. There are several key points:
 1. Cardiac syncope carries a high mortality rate, and physicians should **admit any individual suspected of having cardiac syncope** for evaluation.
 2. **Syncope in the elderly** is frequently multifactorial (e.g., drugs, structural heart disease, anemia, volume depletion, and decreased baroreceptor sensitivity).
 3. The **workup should be individualized** to be cost-effective and accurate, as shown in Figure 33.1.
- B. **Echocardiography** is routinely used for diagnosing patients with syncope who are suspected of having cardiac disease. The echocardiogram is useful in diagnosing valve pathology and myocardial processes that may contribute to syncope, such as aortic stenosis and cardiac tumors (i.e., myxomas). Some small studies and case reports suggest that echocardiographic data frequently aid in diagnosing a cardiac origin for syncope. However, larger studies have shown that the diagnostic yield of echocardiography is quite low in the absence of clinical, physical, or electrocardiographic findings, suggesting a cardiac abnormality. In patients with syncope or presyncope and a normal physical examination, mitral valve prolapse is the most common finding.

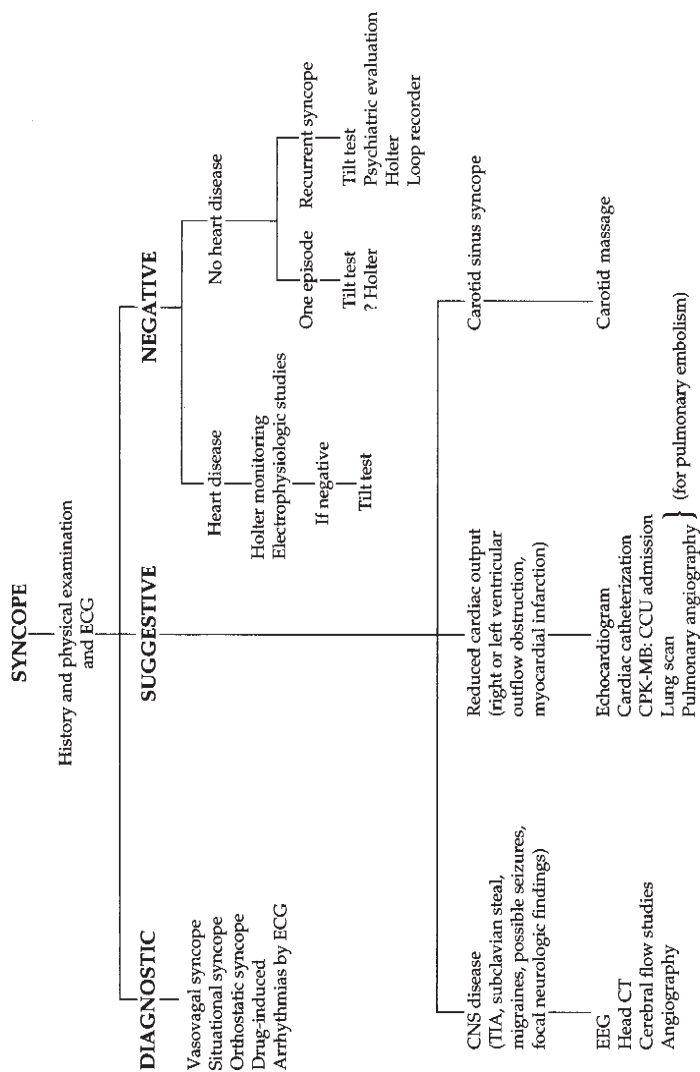


FIGURE 33.1 Schematic algorithm for the evaluation of patients presenting with syncope. ECG, electrocardiogram; CNS, central nervous system; TIA, transient ischemic attack; EEG, electroencephalogram; CT, computed tomography; CPK-MB, creatine phosphokinase-myocardial band; CCU, coronary care unit. (From Kapoor WN. Diagnostic evaluation of syncope. *Am J Med.* 1991;90:91–106, with permission.)

- C. Holter monitoring.** Holter or prolonged electrocardiographic monitoring is one of the most commonly used tests for the evaluation of syncope. However, symptomatic correlation of a cardiac arrhythmia with a syncopal spell occurs in only about 4% of cases. **A completely normal or negative Holter result may be just as helpful as a captured arrhythmia.** The sensitivity and specificity of electrocardiographic monitoring for arrhythmic syncope are not known because of the lack of criteria for abnormal results or a gold standard that is independent of arrhythmias diagnosed by monitoring. The difficulty is to establish a correlation between arrhythmia and asyncope spell.
1. Gibson et al. reviewed 1,512 Holter recordings of patients referred for evaluation of syncope; a total of 255 (17%) patients reported syncope or related symptoms, of which only 30 (2%) were correlated with arrhythmias. Ventricular tachycardia was predominant in the syncope group, whereas supraventricular and sinus tachycardia were common in the presyncope group. There was an increasing incidence of supraventricular and ventricular tachycardia with age, but the correlation with syncope remained obscure.
 2. Pratt et al. studied 80 patients with structural heart disease were investigated by Holter monitors and follow-up EP study. The authors concluded that the combination of a clinical presentation of syncope, presence of coronary artery disease, and left ventricular ejection fraction < 30% had a better positive predictive value in terms of inducibility of sustained ventricular tachycardia than any ambulatory electrocardiographic monitoring criteria.
 3. Studies have shown that **sinus pauses longer than 2 seconds, second-degree atrioventricular block (type II) or complete atrioventricular block, and runs of nonsustained ventricular tachycardia on Holter monitoring should be taken seriously.**
 4. The duration of electrocardiographic monitoring is an important issue. It appears that **48 hours is optimal.**
- D. Loop recorder.** When used correctly, **loop recorders effectively couple arrhythmias and syncope.** Loop recorders are **useful in patients with recurrent frequent syncope**, who benefit from prolonged monitoring for weeks to months. When activated by the patient, loop recorders permanently record the previous 4 to 5 minutes of rhythm data. The recorder can capture arrhythmias during a syncopal episode if the patient activates it after regaining consciousness. The next-generation loop recorders (e.g., Medtronic-Reveal) are implantable devices similar to a pacemaker. They continuously record a single-lead ECG. These devices have the capability to store a 15-minute segment of cardiac rhythm when activated during or after a syncopal episode by the patient and can also be programmed to automatically begin recording when triggered by a high or low heart rate.
- Two randomized clinical trials have shown that implantable loop recorders (ILRs) are more likely to lead to a diagnosis of syncope than conventional management. In the Randomized Assessment of Syncope Trial (RAST), 60 patients were randomized to receive either an ILR or conventional testing. A diagnosis was made in 52% of the patients with an ILR and in only 20% of the patients receiving conventional testing ($p = 0.012$). In the Eastbourne Syncope Assessment Study (EaSyAS), 201 patients were randomized to receive an ILR or conventional diagnostic testing. An ECG diagnosis of syncope was established in 33% of the patients with ILR but in only 4% of the conventional strategy patients ($p < 0.0001$).
- E. SAECG** is useful in predicting inducibility of ventricular arrhythmias by EP testing, especially in patients with ischemic heart disease. However, it is not helpful in diagnosing sinus pauses or atrioventricular block. Most patients with syncope in the setting of structural heart disease are likely to require an EP study or implantation of a defibrillator if left ventricular dysfunction or coronary artery disease is present. SAECG may, therefore, be more appropriately employed in patients with

structurally normal hearts to predict whether an EP study is indicated. SAECG may also be helpful in identifying patients with arrhythmogenic right ventricular dysplasia or infiltrative cardiomyopathies.

1. **SAECG** is a collection of 100 to 300 single QRS complexes, which are amplified, filtered for noise, and averaged to determine the presence of late potentials. Late potential refers to the presence of low-amplitude, high-frequency signals in the terminal segment of the amplified QRS. **The late potentials seem to identify the presence of a reentrant substrate and may indicate an independent risk for the development of future life-threatening ventricular arrhythmias.**
 2. **When combined with an ejection fraction of < 40%, the presence of late potentials can be used to identify patients with an even higher risk of ventricular tachycardia.** Studies evaluating this profile of patients have demonstrated sensitivity of 90% and specificity of 95% to 100% in predicting inducible, sustained ventricular tachycardia.
 3. Various commercially available devices use different filters, lead configurations, and processing algorithms; therefore, **the criteria for abnormal SAECG may vary among manufacturers.** Abnormal SAECG findings include total QRS duration > 114 milliseconds, root mean square voltage of the terminal 40 milliseconds of the complex (RMS40) < 20 μ V, or duration of low-amplitude signals (LASs) in terminal QRS (LAS) > 38 milliseconds. The total duration of the QRS complex, including the late potential, is independent of other measures of cardiac risk. RMS40 is probably the most sensitive and specific of all three variables.
 4. **A positive SAECG finding suggests the need for further EP testing,** especially in individuals with known heart disease.
 5. **The absence of late potentials has a high negative predictive value (94%).** In patients with syncope and a negative SAECG result, EP study is not absolutely indicated. A normal SAECG result is associated with a < 5% risk of inducible ventricular tachycardia on EP testing.
 6. **No satisfactory method of analysis is available for patients with bundle branch block,** because it is virtually impossible to distinguish between late activation due to the conduction defect and that due to the reentrant substrate.
- F. EP study.** EP study should be considered in **patients with underlying structural heart disease or in elderly patients with recurrent syncope.** Similar to Holter monitoring, induced arrhythmias during EP study do not usually produce syncope in the laboratory; therefore, a cause-and-effect relationship often has to be assumed. Regardless, EP testing is useful in better delineating a cardiac cause of syncope, especially in people with baseline bundle branch or bifascicular block.
1. **Indications** for EP study generally include the following:
 - (a) Known or suspected ventricular tachyarrhythmias, especially to guide therapy
 - (b) Uncertainty about the origin of wide QRS tachycardia
 - (c) Patients with unexplained syncope and history of heart disease
 - (d) Patients with nonsustained ventricular tachycardia, impaired left ventricular function, and late potentials on SAECG, used to stratify prognosis and guide therapy
 - (e) Patients with drug-refractory malignant ventricular arrhythmias who are candidates for ablative therapy
 2. Some **EP findings** are considered important in the cause of syncope:
 - (a) Sustained monomorphic ventricular tachycardia
 - (b) Sinus node recovery time longer than 3 seconds
 - (c) Spontaneous or pacing-induced infranodal block or infrahisian block
 - (d) Baseline His-ventricle (HV) interval > 100 milliseconds or significant prolongation after procainamide challenge
 - (e) Paroxysmal supraventricular tachycardia with symptomatic hypotension

3. The sensitivity and specificity of induced, sustained monomorphic ventricular tachycardia are > 90%. However, the sensitivity of prolonged sinus node recovery time is low (69%), although the specificity is reported to be as high as 100% when EP studies are compared with results of Holter monitoring.
4. Patients with no known heart disease, ejection fraction > 40%, normal electrocardiographic and Holter results, and multiple syncopal episodes (more than five per year) often have **negative EP study results**. A 3-year follow-up of patients with negative EP test results revealed a 24% recurrence rate of syncope and a mortality rate of 15%; however, **a 3-year follow-up after positive EP study results and treatment revealed a 32% recurrence rate and higher mortality (61%)**.
5. For patients with coronary artery disease and syncope who have mild to moderate left ventricular dysfunction (left ventricular ejection fraction, 35% to 50%), inducible ventricular tachycardia during an EP study is unlikely, but the study is often appropriate, given the significant implications of a positive test.
6. Patients with stable coronary artery disease and severe left ventricular dysfunction (< 35%) have substantial benefits once treated with an ICD. Hence, an EP study is often not required.
7. Patients with severe nonischemic dilated cardiomyopathy (EF < 40%) and New York Heart Association (NYHA) class II–III symptoms do not benefit from an EP study, and there is no evidence to support the use of antiarrhythmic medications in these patients. Evidence from the Defibrillators in Non-ischemic Cardiomyopathy Treatment Evaluation (DEFINITE) trial and Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) supports the mortality benefit from ICD implantation in these patients with heart failure symptoms. Moreover, patients with wide QRS (> 120 milliseconds) and severe cardiomyopathy with NYHA class II–III symptoms benefit symptomatically from cardiac resynchronization therapy (CRT) and have an improvement in mortality compared with antiarrhythmic medications by receiving a CRT-defibrillator device.
8. **The limitations and disadvantages of EP testing** are high cost, invasive nature, lower specificity if a more aggressive electrical stimulation protocol is used, and poor prediction of bradyarrhythmias and several other arrhythmias of unknown clinical significance without symptoms. A detailed discussion of EP studies is provided in Chapter 63.

G. Upright tilt table testing

1. **Mechanism.** It is believed that a surge in catecholamines may paradoxically enhance the susceptibility to bradycardia and hypotension, resulting in syncope by the activation of cardiac mechanoreceptors. Vasovagal syncope can be induced by keeping susceptible individuals upright on a tilt table with or without chemical stimulation. The mechanism is not completely understood, but it is believed to be similar to the activation of the Bezold-Jarisch reflex.
2. The best candidate for a tilt table study is a **person with unexplained recurrent syncope, with underlying heart disease and a negative EP study or with no known structural heart disease**. In reviewing various tilt table studies, Kapoor et al. (2) found that 49% of patients had a positive response during tilt table testing, 66% had a positive response using isoproterenol with tilt table testing, 65% had a cardioinhibitory response, and 30% had a vasodepressor response. The **number of positive responses increased with an increasing angle of tilt and longer duration**; however, there was no correlation between positive responses and maximum dose of isoproterenol. Although limited information is available on the sensitivity of upright tilt table testing, it is reported to be about 70%. The specificity has ranged from 35% to 92% with isoproterenol. Kapoor et al. (2) reported higher false-positive rates with isoproterenol, especially at higher angle of tilt, indicating lower specificity.

3. It appears that **tilt table testing, when used in the appropriate setting, is beneficial in diagnosing previously unexplained syncope**, preventing recurrences, and reducing morbidity.

H. Adenosine triphosphate (ATP) test. The intravenous injection of ATP has been suggested to aid in the diagnosis of unexplained syncope. Patients are injected with a 20-mg bolus of ATP and are kept in a supine position with continuous electrocardiographic monitoring. Asystole lasting more than 6 seconds or atrioventricular block lasting longer than 10 seconds is considered abnormal. In patients with unexplained syncope, the ATP test may be able to diagnose syncope caused by transient atrioventricular block. However, it has not been able to reproduce sinus arrest. This test remains in the investigational phase, and outcome data are not yet available.

IV. TREATMENT. Treatment of syncope is individualized and depends on the underlying cause.

A. Nonpharmacologic therapy. The treatment of syncope hinges on preventing recurrent episodes and lowering mortality. The neurally mediated reflex syncopal syndromes can be treated in part by behavior modification. Initial measures aimed at reducing these syncopal events include advising patients to avoid precipitating triggers. Patients should also be counseled on the avoidance of volume depletion. Medication regimens such as chronic vasodilator therapy may predispose to syncope and should also be avoided. Moderate exercise training, tilt training, and increased intake of salt and electrolytes are some initial measures that help in reducing vasovagal syncope.

Small trials have shown a benefit from tilt training and counterpressure maneuvers to prevent neurally mediated syncope. In tilt training, patients are subjected to progressively longer periods of upright posture in order to condition the neural and vascular systems to counter gravitational stress. In one small study of 42 patients with neurally mediated syncope, tilt training resolved symptoms in 36 patients during the period of training. Counterpressure maneuvers are isometric arm and leg exercises that patients perform at the first sign of a syncopal episode. These maneuvers raise peripheral vascular resistance and blood pressure and can prevent the syncopal spell. In one trial of 21 patients, patients were trained to perform isometric leg exercises during a tilt table test. The maneuver successfully raised blood pressure and prevented syncope during the tilt table test, and at follow-up in 10 months, 13 of 20 patients continued to use the maneuver in daily life. These treatments are often used as first-line therapy for neurally mediated syncope.

B. Medical therapy. Most long-term, randomized studies testing the utility of using medications to prevent syncope, including those of β -blockers, have failed to show any benefit over placebo, and these treatments are generally considered second line. Table 33.4 lists the various causes of syncope and potential medical treatment.

1. **Electrolyte abnormalities must be corrected** if they are suspected as the cause of arrhythmias (e.g., prolonged QT from hypomagnesemia or hypocalcemia).
2. **Particular attention should be given to the patient's medications**, since they may have drug-drug interactions or proarrhythmic potential that may cause orthostatic hypotension. Unnecessary medications should be discontinued.

C. Device therapy

1. **Symptomatic bradyarrhythmias and atrioventricular blocks require pacemaker implantation**

- a. Patients with an HV interval (i.e., impulse time from atrioventricular node to the ventricle) of > 100 milliseconds are at a high risk for **progression to heart block** and may benefit from a pacemaker.
- b. Although the mode of pacing is debated, in **patients with carotid sinus syncope**, a dual-chamber pacer with rate responsiveness is most desirable.

TABLE 33.4 Medical Therapy in Syncope

Cause	Treatment
Vasodepressor syncope	β -Blockers, disopyramide CR 200 mg bid, fluoxetine 20–80 mg daily, sertraline 50–200 mg daily, dual-chamber pacing, theophylline ER 300–600 mg daily, and scopolamine hydrobromide 0.4–0.8 mg bid–tid
Dysautonomic syncope	Elastic support hose, water exercise, increased sodium intake, fludrocortisone 0.05–0.2 mg daily, ephedrine sulfate 25–50 mg tid, midodrine 5–10 mg tid, erythropoietin, and methylphenidate 5–20 mg bid–tid
Situational syncope	Stool softeners, urinating while sitting down
Carotid sinus syncope	Avoidance of tight collars, surgical removal of carotid sinus tumor, pacemaker in patients with predominantly cardioinhibitory syncope
Tachyarrhythmias	Implantable defibrillators or trial of antiarrhythmic agents

CR, controlled release; ER, extended release.

Adapted from Kapoor WN, Smith M, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med.* 1994;97:78–88.

- c. Dual-chamber pacing has reduced the short- and long-term likelihood of syncope in highly selected patients with recurrent vasovagal syncope. In patients with recurrent vasovagal syncope, dual pacing with hysteresis should be considered an option if other treatment modalities have been ineffective.
- 2. **Antiarrhythmic therapy** appears to decrease the frequency of syncope; however, it has not been shown to improve survival. In patients with malignant or life-threatening ventricular arrhythmias or inducible, sustained monomorphic ventricular tachycardia, **implantable defibrillators** are the best option based on study findings, especially in patients with unexplained syncope who have a history of coronary artery disease and severe left ventricular dysfunction.

D. Surgical therapy

1. **Patients who have exertional cardiac syncope** due to left or right heart outflow obstruction, such as HOCM, should be instructed to **avoid exertional activities** that precipitate syncope and **should be considered for surgical repair**.
2. Surgical septal myectomy is the procedure of choice in **patients with HOCM**; however, percutaneous septal ablation with alcohol is an alternative in patients who are considered at high surgical risk.
3. Coronary artery bypass grafting or percutaneous coronary intervention is strongly indicated in **patients with life-threatening arrhythmias (usually polymorphic ventricular tachycardias) due to myocardial ischemia**.

V. FOLLOW-UP. The follow-up of patients with syncope often depends on the cause and the therapy being instituted.

- A. **Patients with frequent spells of syncope without an identifiable cause** should be considered for more extensive monitoring such as ILRs, because they may have an undiagnosed cardiac cause.
- B. **Patients with cardiac syncope** require very close follow-up because their mortality rates are significantly higher than those of patients with other causes of syncope.

- C. **Elderly patients** may require closer monitoring about their home situation, their need for assistance with activities of daily living, and changes in medications.
- D. A consultant who diagnoses syncope should **communicate with the patient's primary physician about cause, therapy, and important warning signs** if devices such as pacemakers or defibrillators are implanted.
- E. **Hospitalization.** The decision about which patients to hospitalize can be complex. The underlying heart disease has been found to be the most important factor in determining prognosis and risk stratification, and it mandates hospitalization for the evaluation of syncope. Patients without evidence of structural heart disease who have a normal ECG and a high probability of having neurally mediated syncope are at low risk and generally have good long-term outcomes. Outpatient evaluation of syncope may be appropriate for these patients in many instances. Physicians should also consider hospitalization for patients with exertional syncope, syncope causing severe injury, and those with a strong family history of sudden death.

Risk scores have been developed to help predict which syncope patients are at risk for a serious outcome and should be considered for hospitalization. One of these, the San Francisco Syncope Rule, can be remembered by the mnemonic CHES (history of chronic heart failure, hematocrit < 30%, abnormal ECG, shortness of breath, systolic blood pressure < 90 mm Hg). This risk score was derived from a group of 684 syncope patients who presented to the emergency department of a university hospital. Use of this score identified patients at risk of a serious outcome with 96% sensitivity and 62% specificity.

VI. POSTURAL ORTHOSTATIC TACHYCARDIA SYNDROME (POTS). POTS is an emerging and still poorly understood syndrome in which patients feel an exaggerated increase in heart rate with tilt and exercise. They may also feel fatigue, dyspnea, and light-headedness on standing, but do not typically experience orthostatic hypotension or syncope. The disorder is the most common syndrome seen in young people referred to autonomic dysfunction clinics and is thought to affect 500,000 Americans. Patients typically present at age 14 to 45 years and are usually female (female to male ratio of 4 to 5:1). Patients often have multisystem complaints such as fibromyalgia, chronic fatigue syndrome, sleep disorders, and gastrointestinal symptoms, suggesting a diffuse autonomic dysfunction.

A. Etiology. POTS is thought to be a syndrome with multiple overlapping etiologies, with each etiology having varying importance in individual patients.

1. **Partial dysautonomia** refers to autonomic impairment in some parts of the nervous system, with efforts by the still-functioning nervous system to compensate. A number of studies have shown findings of distal denervation in POTS patients, including the following:
 - (a) Lower extremity anhidrosis.
 - (b) Impaired norepinephrine spillover in the legs. The rate of entry of norepinephrine into the femoral vein is reduced in response to hypotensive stimuli.
 - (c) A decrease in muscle sympathetic nerve activity recruitment in the legs in response to nitroprusside-induced hypotension.
2. **Increased sympathetic activity.** Studies have shown that patients with POTS have elevated arterial norepinephrine levels and decreased norepinephrine clearance. Some patients also have increased resting heart rates and an exaggerated response to isoproterenol, suggesting adrenoceptor hypersensitivity.
3. **Hypovolemia.** Studies have shown reduced blood volume and reduced erythrocyte volume. The cause of these findings is not clear, but some have postulated problems with the renin–angiotensin–aldosterone axis, possibly due to renal denervation.
4. **Changes in venous function.** Patients with POTS have been shown to have increased venous pooling and a decrease in stroke volume on standing.
5. **Primary baroreflex abnormalities** may also cause the increase in heart rate without change in blood pressure that is seen on standing.

- B. Diagnosis.** There are no established criteria for the diagnosis of POTS. The characteristic finding is an increase in heart rate on tilt table testing or standing. Many centers use an increase in heart rate of > 30 beats per minute or a rise in heart rate to > 120 beats per minute in the first 10 minutes of tilt as their diagnostic criteria. Orthostatic hypotension does not typically occur. There may be an increase in plasma norepinephrine levels (> 600 ng/mL), both with rest and on standing. It is important to rule out other conditions, such as autonomic neuropathy, central dysautonomia, bedrest deconditioning, dehydration, and medication effects that may also cause these findings.
- C. Treatment.** Because of the heterogeneous etiologies of POTS, which contribute differently to each patient's symptoms, treatment can be very challenging and often requires multiple attempts with different regimens. There are no large controlled studies of therapy.
1. Volume expansion using oral fluid intake, a high salt diet, and the mineralocorticoid fludrocortisone can improve symptoms. This treatment can cause hypertension, fluid retention, and hypokalemia, and patients should be monitored closely.
 2. Adrenoreceptor agonists such as midodrine may improve symptoms in patients with mainly peripheral autonomic denervation. Studies have shown improvement in heart rate response and symptoms during tilt testing with these treatments.
 3. Patients with mainly hyperadrenergic symptoms may see improvement with β -blockers. In one placebo-controlled, randomized crossover study, low-dose propranolol (20 mg) improved tachycardia and reduced symptoms, but high-dose propranolol (80 mg) did not change or worsened symptoms.
 4. Pyridostigmine, an acetylcholinesterase inhibitor, has been used to attenuate tachycardia.
 5. Other centrally acting drugs, such as selective serotonin reuptake inhibitors, clonidine, methyl dopa, and phenobarbital, have been used with some success, but experience with their use is very limited.

ACKNOWLEDGMENTS: *The author thanks Drs. Carlos Alves, Keith Ellis, and Vasant B. Patel for their contributions to earlier editions of this chapter.*

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CHAPTER

34

Chetan Vagesh Hampole

Assessing and Managing Cardiac Risk in Noncardiac Surgical Procedures

I. INTRODUCTION

- A. Background.** Patients undergoing noncardiac surgeries can be at risk for major perioperative cardiac complications, particularly if they are elderly. Worldwide, it is estimated that approximately 500,000 to 900,000 patients per year undergoing noncardiac surgery suffer a perioperative cardiac death, nonfatal myocardial infarction (MI), or nonfatal cardiac arrest. Given the increasingly advanced age of patients undergoing surgeries, this risk is expected to remain substantial. The risk of death from a perioperative MI may be as high as 50%. The elevated risk of perioperative MI is multifactorial and may be primarily due to increased sympathetic tone, a proinflammatory state,

hypercoagulability, and occasional hypoxia during the first few days after surgery. In 1977, Goldman et al. (1) developed a multifactorial index of risk for cardiac morbidity and mortality. Extensive work has subsequently been done on various aspects of perioperative cardiac evaluation, including clinical factors and noninvasive testing. The variety of strategies and practices used has led to high costs associated with preoperative risk assessment. Many studies have recently challenged common practices in the area of perioperative care that were found to have no clear benefit. The American College of Cardiology/American Heart Association (ACC/AHA) Task Force Committee developed practice guidelines aimed at providing a more efficient approach to preoperative evaluation. These guidelines were most recently updated in 2007.

- B. Objective.** The purpose of preoperative evaluation is not to “clear” patients for an operation. The purpose is to **assess current medical status and cardiac risks posed by the planned operation** and **recommend strategies that may influence short- and long-term outcomes**.
1. Although the preoperative assessment is a complex process, a few **basic questions and observations** by a physician with regard to the patient’s general health, functional capacity, cardiac risk factors, comorbid medical illnesses, and type of anticipated operation can assist in evaluating cardiac risk.
 2. It is not prudent to order noninvasive tests for every patient. The physician tries to obtain as much information as possible by means of **history and physical examination**. Noninvasive tests are requested only if the results are likely to influence treatment and outcome.
 3. **As a general rule, preoperative intervention is rarely needed unless it is indicated irrespective of the preoperative context.** Patients with clinically stable heart disease may not need extensive preoperative testing.
 4. Communication is vital among primary physicians, consulting physicians, anesthesiologists, and surgeons for short- and long-term care of patients.

II. CLINICAL PRESENTATION

A. History

1. The clinician needs to identify cardiac conditions that place a patient at increased risk, such as recent MI, decompensated congestive heart failure (CHF), unstable angina, significant arrhythmias, and valvular heart disease.
2. Attention is directed at serious **comorbid conditions** such as diabetes mellitus, peripheral vascular disease, history of stroke, renal disease, and pulmonary disease.
3. **Functional capacity** is determined on the basis of the patient’s ability to perform certain daily tasks (Table 34.1).

B. Physical findings.

A thorough examination is crucial, and specific findings are addressed.

1. The physical examination includes checking blood pressure in both arms (supine and standing) and evaluation of carotid arterial pulse (character, volume, and upstroke), jugular venous pulsation, cardiac rhythm, heart sounds (murmurs, gallops, or rubs), and extremity pulses.
2. Lung fields are auscultated, and the abdomen is palpated for a possible aneurysm.
3. **High-risk findings** include severe aortic stenosis murmur, elevated jugular venous pressure, pulmonary edema, or S_3 gallop.

C. Indices to predict cardiac risk.

Cardiac risk is a function of patient characteristics and the proposed operation.

1. **The Goldman index** was developed in 1977. The index is a score derived from nine independent variables that predict perioperative cardiac events, and each is assigned a point value (Table 34.2).
2. **Detsky et al.** (2) developed a modified multifactorial index to address the severity of coronary artery disease (CAD) and heart failure (Table 34.3).

TABLE 34.1 **Estimated Energy Requirements for Various Activities**

1 to 4 METs

- Eat, dress, or use the toilet
- Walk indoors around the house
- Walk on level ground at 2 mph (3.2 km/h)
- Do light housework such as washing dishes

4 to 10 METs

- Climb a flight of stairs
- Walk on level ground at 4 mph (6.4 km/h)
- Run a short distance
- Heavy work such as vacuuming or lifting heavy furniture
- Play games such as golf or doubles tennis

More than 10 METs

- Participate in strenuous activities such as swimming, singles tennis, basketball, or skiing

MET, metabolic equivalent.

TABLE 34.2 **Original Goldman Multifactorial Cardiac Risk Index**

Criteria	Points
History	
Age older than 70 y	5
MI in previous 6 mo	10
Physical examination	
S ₃ gallop or JVD	11
Significant AS	3
Electrocardiogram	
Rhythm other than sinus or PACs on last preoperative ECG	7
Greater than 5 PVCs/min documented at any time preoperatively	7
General status (one or more of the following)	
Po ₂ < 60 or Pco ₂ > 50 mm Hg, K < 3.0 or HCO ₃ < 20 mEq/L, BUN > 50 or Cr > 3.0 mg/dL; abnormal AST, signs of chronic liver disease, or patient bedridden from noncardiac causes	3
Operation	
Intraperitoneal, intrathoracic, or aortic operation	3
Emergency operation	4
Total	53

(continued)

TABLE 34.2 Original Goldman Multifactorial Cardiac Risk Index (*continued*)

Class	Points	Cardiac deaths (%)
I	0–5	0.2
II	6–12	2.0
III	13–25	2.0
IV	≥ 26	56.0

AS, aortic stenosis; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; ECG, electrocardiogram; JVD, jugular venous distention; MI, myocardial infarction; PAC, premature atrial contraction; PVC, premature ventricular contraction.

Adapted from Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med*. 1977;297:845–850.

TABLE 34.3 Detsky's Modified Cardiac Risk Index

Variable	Points
Coronary artery disease	
MI within 6 mo earlier	10
MI more than 6 mo earlier	5
Canadian class of angina	
Class III	10
Class IV	20
Unstable angina within 3 mo	10
Alveolar pulmonary edema	
Within 1 wk	10
Ever	5
Valvular disease	
Suspected critical aortic stenosis	20
Arrhythmias	
Sinus plus atrial premature beats or rhythm other than sinus on last preoperative electrocardiogram	5
Greater than five ventricular premature beats at any time before operation	5
Poor general medical status^a	5
Age older than 70 y	5
Emergency operation	10
Total	120

^aDefined as any of the following: $PO_2 < 60$ mm Hg, $Pco_2 > 50$ mm Hg, $K^+ < 3.0$, $HCO_3^- < 20$ mEq/L, BUN = 18 mmol/L (> 50 mg/dL), serum Cr > 260 mmol/L (> 2.9 mg/dL), abnormal AST, signs of chronic liver disease, or patient bedridden because of noncardiac causes. AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cr, creatinine; MI, myocardial infarction.

Adapted from Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Gen Intern Med*. 1986;1:211–219.

TABLE 34.4 Revised Cardiac Risk Index**Six independent predictors of major cardiac complications**

High-risk surgery (intrathoracic, intraabdominal, or suprainguinal vascular procedures)

History of ischemic heart disease (history of MI or a positive exercise stress test, current complaint of chest pain thought to be due to MI, use of nitrate therapy, or ECG with pathological Q waves; do not count prior coronary revascularization procedure unless one of the other criteria for ischemic heart disease is present)

History of heart failure

History of cerebrovascular disease

Diabetes mellitus requiring insulin therapy

Serum creatinine > 2.0 mg/dL (177 μmol/L)

Rate of cardiac death, nonfatal MI, and nonfatal cardiac arrest according to the number of predictors

No risk factors: 0.4% (95% CI, 0.1–0.8%)

One risk factor: 1.0% (95% CI, 0.5–1.4%)

Two risk factors: 2.4% (95% CI, 1.3–3.5%)

Three or more risk factors: 5.4% (95% CI, 2.8–7.9%)

Rate of cardiac death and nonfatal MI, cardiac arrest or ventricular fibrillation, pulmonary edema, and complete heart block according to the number of predictors and the nonuse or use of β-blockers

No risk factors: 0.4–1.0% versus < 1% with β-blockers

One to two risk factors: 2.2–6.6% versus 0.8–1.6% with β-blockers

Three or more risk factors: > 9% versus > 3% with β-blockers

Adapted from Lee TH, Marcantonio ER, Mangione CM et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043–1049.

3. In 1999, **Lee et al. (3) developed the Revised Cardiac Risk Index** to simplify the process using only six risk factors (Table 34.4). This is now the most widely used risk index and is the one incorporated in the ACC/AHA guidelines.
- D. Clinical assessment of risk factors.** Instead of dividing risk factors into major, intermediate, and minor groups, the new 2007 ACC/AHA guidelines adopted a more practical approach by recognizing the following conditions:
 1. **Active cardiac conditions.** The presence of one or more of these conditions warrants intensive evaluation and management before proceeding with noncardiac surgery and may result in delay or cancellation of the scheduled surgery (Table 34.5).
 2. **Clinical risk factors.** With the exception of the type of surgery, these factors are the same risk factors identified by the Revised Cardiac Risk Index (Table 34.4), and they include the following:
 - (a) History of ischemic heart disease
 - (b) History of compensated or prior heart failure
 - (c) History of cerebrovascular disease
 - (d) Diabetes mellitus
 - (e) Renal insufficiency
 3. The original guidelines recognized a group of **minor** predictors that included advanced age, abnormal electrocardiogram (ECG), rhythm other than sinus, and

TABLE 34.5 Active Cardiac Conditions That Warrant Evaluation and Treatment before Noncardiac Surgery
Unstable coronary syndromes

Acute or recent myocardial infarction^a

Unstable or severe^b angina (Canadian class III or IV)^c

Decompensated heart failure
Significant arrhythmias

High-grade atrioventricular block

Mobitz type II atrioventricular block

Third-degree atrioventricular block

Symptomatic ventricular arrhythmias

Supraventricular arrhythmias (including atrial fibrillation) with uncontrolled ventricular rate

Symptomatic bradycardia

Newly recognized ventricular tachycardia

Severe valvular disease

Severe aortic stenosis (mean pressure gradient ≥ 40 mm Hg, aortic valve area ≤ 1.0 cm², or symptomatic)

Symptomatic mitral stenosis

^aThe American College of Cardiology National Database Library defines acute MI as within 7 d and recent MI as > 7 d and ≤ 1 mo.

^bMay include stable angina among patients who are unusually sedentary.

^cData from Campeau L. Grading of angina pectoris. *Circulation*. 1976;54:522–523.

Adapted from Fleisher LA, Beckman JA, Brown KA et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;50:1707–1732.

uncontrolled hypertension. **Although the presence of many of these factors might lead to a *higher suspicion of CAD*, they have *not* been shown to increase perioperative risk independently, and therefore, they are no longer incorporated into the recommendations for treatment.**

III. TYPE OF OPERATION. In addition to clinical markers and functional capacity, **the proposed operation is an important factor, especially among patients with multiple clinical risk factors** (Table 34.6). The consultant uses all the information available to estimate cardiac risk and provides recommendations to minimize perioperative risk. For **surgical emergencies**, the patient should **proceed directly to the operating room**; emphasis in these circumstances is on postoperative evaluation and management. For **urgent surgical procedures**, evaluation must be **tailored to the underlying disease process**. Elective procedures allow for more thorough evaluation, and all care should be taken to minimize risk. **Testing is limited exclusively to those studies whose results might change management.**

TABLE 34.6 Cardiac Risk Stratification by the Type of Surgical Procedure**High-risk procedure (cardiac risk > 5%)**

Aortic and other major vascular surgery (endovascular abdominal aortic aneurysm repair is considered intermediate risk) and peripheral vascular surgery (carotid endarterectomy is considered intermediate risk)

Intermediate-risk procedure (cardiac risk 1–5%)

Carotid endarterectomy and endovascular abdominal aortic aneurysm repair

Head and neck surgery

Intraperitoneal surgery

Intrathoracic surgery

Orthopedic surgery

Prostate surgery

Low-risk procedure (cardiac risk < 1%)

Breast surgery

Cataract surgery

Endoscopic procedures

Superficial procedures

Ambulatory surgery

Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol*. 2007;50:1707–1732.

IV. SUPPLEMENTAL PREOPERATIVE EVALUATION

- A. Routine laboratory tests** such as serum creatinine, hemoglobin, platelets, potassium, liver profile, and oxygen saturation are important in determining whether a patient needs special attention. Such patients include those with bleeding risk, renal failure, or liver disease.
- B.** Patients with **pulmonary disease** (i.e., chronic obstructive pulmonary disease or pulmonary fibrosis) undergo a preoperative **arterial blood gas evaluation**.
- C.** A 12-lead **ECG** is recommended for patients with at least one clinical risk factor who are undergoing vascular surgery and for patients with known history of CAD, peripheral vascular disease, or cerebrovascular disease who are undergoing an intermediate-risk surgical procedure. A 12-lead ECG is also reasonable in patients with no clinical risk factors who are undergoing vascular surgery and, possibly, in patients with at least one clinical risk factor who are undergoing intermediate-risk surgery.
- D. Echocardiography.** Echocardiograms can provide information about certain pathologic conditions (left ventricular dysfunction and aortic stenosis) that predispose to increased perioperative cardiac risk. However, the routine use of echocardiography is not helpful and should be reserved for patients who meet ACC/AHA clinical guidelines or for patients in whom the physical examination is suggestive of aortic stenosis, regardless of the planned surgery.

V. STEPWISE APPROACH TO PREOPERATIVE CARDIAC ASSESSMENT. The ACC/AHA Task Force developed an **algorithm for preoperative cardiac evaluation** to help physicians systematically identify clinical predictors and determine if noninvasive testing is indicated prior to the noncardiac surgery (Fig. 34.1).

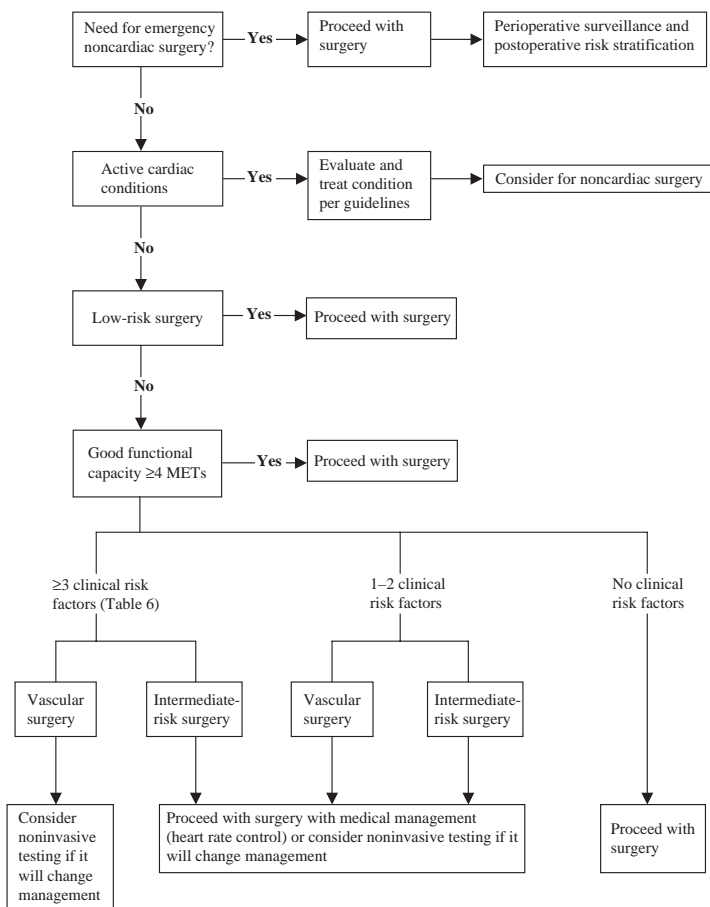


FIGURE 34.1 A stepwise approach to preoperative cardiac evaluation of a patient undergoing a noncardiac surgery. (Adapted from Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 Guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines [Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery]. Developed in Collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Heart Rhythm Society, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, and Society for Vascular Surgery. *J Am Coll Cardiol.* 2007;50:1707–1732.)

VI. NONINVASIVE CARDIAC STRESS TESTING. The ability of noninvasive cardiac tests to predict perioperative risk is uncertain. Recently, there has been increasing evidence discouraging the need for their routine use in patients undergoing preoperative evaluation. This shift away from noninvasive testing was supported by the results of a randomized controlled trial of preoperative myocardial revascularization in vascular surgery patients that showed no improvement in perioperative or long-term outcomes associated with prophylactic revascularization. Another study challenged the old ACC/AHA guidelines by randomizing stable intermediate-risk patients undergoing major vascular surgery between cardiac stress testing strategy and no testing. By using excellent β -blocker therapy with tight heart rate control of 60 to 65 beats/min, there was no significant difference in the primary end point (composite postoperative cardiac death and/or nonfatal MI) between preoperative cardiac testing and no testing strategies. Therefore, **preoperative noninvasive cardiac testing should be reserved for patients who are candidates for these tests according to guidelines and who based on the results of these tests could potentially be considered for angiography and revascularization regardless of the planned surgery.**

These findings were reflected in the new ACC/AHA 2007 guidelines:

- (A) Patients with **active** cardiac conditions (Table 34.5) should be **evaluated and treated before noncardiac surgery** (class I).
- (B) In patients with **poor (< 4 metabolic equivalents of the task) or unknown functional capacity**, who have **three or more clinical risk factors** and are undergoing **vascular surgery**, noninvasive **testing is reasonable if it will change management** (class IIa).
- (C) In patients with poor or unknown functional capacity who have one to two clinical risk factors and who are undergoing intermediate-risk surgery, noninvasive testing may be considered (class IIb).
- (D) In patients with good functional capacity who have one to two clinical risk factors and who are undergoing vascular surgeries, noninvasive testing may be considered (class IIb).
- (E) **Noninvasive testing is not** useful in patients **without** clinical risk factors who are undergoing **intermediate-risk surgery**.
- (F) **Noninvasive testing is not useful in patients who are undergoing low-risk surgery.**

There are **different modalities for stress testing**, including exercise ECG, exercise or pharmacologic nuclear stress testing, and exercise or pharmacologic stress echocardiography. When ordering these tests, **it is important to remember the following:**

- (A) When feasible, **exercise is the modality of choice** for stress testing because it provides an objective assessment of functional capacity. Pharmacologic stress testing (adenosine, dipyridamole, and dobutamine) should be reserved for patients who cannot exercise.
- (B) Exercise and pharmacologic stress testing have **excellent negative predictive values** (90% to 100%) **but poor positive predictive values** (6% to 67%), meaning that although a negative study is reassuring, a positive one is still a relatively weak predictor of a perioperative cardiac event.
- (C) Intravenous dipyridamole and adenosine should be avoided in patients with significant bronchospasm or critical carotid artery stenosis.
- (D) Dobutamine should be avoided in patients with significant arrhythmias, severe hypertension, or hypotension.
- (E) **Stress echocardiography** (exercise or dobutamine) offers the advantage of providing additional information about ventricular and valvular function.

VII. PREOPERATIVE CORONARY REVASCULARIZATION. The original ACC/AHA guidelines state that the indications for revascularization before noncardiac surgery should be similar to those in the general population. In other words, there is **no evidence to**

support the role of “prophylactic” preoperative revascularization, and the decision to pursue revascularization should be the same regardless of the planned surgery. However, these statements have been based on expert opinion, and there has been substantial variability among clinicians concerning general practice with cardiac revascularization preoperatively. The **Coronary Artery Revascularization Prophylaxis (CARP) trial** was the first large randomized trial that addressed this issue. It randomized 510 patients with established CAD, who were deemed to be at high risk for perioperative cardiac complications, to undergo either revascularization (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]) or no revascularization before elective major vascular surgery. After a median follow-up of 2.7 years, the death rates were the same in both groups. Even among the subsets of patients who were considered to be at especially high risk according to imaging results or by the Revised Cardiac Risk Index, there were no differences in outcomes between the two groups. Although the study was not designed to test short-term benefit of prophylactic revascularization, there was also no reduction in early postoperative cardiac complications.

Patients who undergo **PCI** represent a clinical challenge in terms of managing their antiplatelet therapy at the time of noncardiac surgery. Premature discontinuation of antiplatelet therapy (aspirin and clopidogrel) carries the risk of in-stent thrombosis. **Bare metal stent (BMS)** thrombosis is most common in the first 2 weeks after stent placement and is very rare after 4 weeks due to rapid endothelialization. On the other hand, there has been growing concern that drug-eluting stent (**DES**) carries greater risk for in-stent thrombosis compared with BMS. The optimal period to delay noncardiac surgery after the use of DES remains unclear.

- A. The **indications for revascularization (CABG or PCI) before noncardiac surgery should be similar to those in the general patient population irrespective of the planned surgery:**
 - (1) Stable angina with known left main disease
 - (2) Stable angina with three-vessel disease (especially with ejection fraction [EF] < 50%)
 - (3) Stable angina with two-vessel disease with significant proximal left anterior descending artery stenosis and either EF < 50% or ischemia on noninvasive testing
 - (4) High-risk unstable angina or non-ST-segment elevation MI
 - (5) Acute ST-elevation MI
- B. Patients with **asymptomatic ischemia** (based on functional study) do not appear to benefit from preoperative revascularization prior to noncardiac surgeries.
- C. Routine prophylactic revascularization should not be performed in patients with stable CAD before noncardiac surgery.
- D. Small observational studies suggest that patients who undergo **CABG** should wait for at least 4 weeks before proceeding with noncardiac surgery.
- E. Patients who undergo **balloon angioplasty without stenting** should wait for **at least 2 to 4 weeks** before proceeding with elective noncardiac surgery to allow adequate time for healing of the injured vessel. Daily aspirin should be continued whenever possible. The risk of stopping aspirin should be weighed against the benefit of reducing bleeding risk from surgery. Balloon angioplasty without the use of stent might provide a temporary bridge to go through noncardiac surgery with the intention of implanting stents after the surgery.
- F. Among patients who undergo stenting with **BMSs**, it is safer to **wait for 6 to 8 weeks** on dual antiplatelet therapy (aspirin and clopidogrel) before proceeding with surgery to avoid the risk of in-stent thrombosis with premature discontinuation of antiplatelet therapy. After 4 to 6 weeks, clopidogrel could be stopped preoperatively, ideally 5 to 7 days before the noncardiac surgery. Daily aspirin use should be continued unless the risk of bleeding outweighs the benefit of continuing aspirin therapy.
- G. Among patients who undergo stenting with the **DES**, the optimal duration for dual antiplatelet therapy is not well defined, but should be **at least 12 months**. Elective

noncardiac surgery that requires discontinuation of clopidogrel, or both clopidogrel and aspirin, should be delayed. In general, if noncardiac surgery is expected within the next 12 months, the physician should strongly consider avoiding the use of DES. BMS or balloon angioplasty might provide an alternative approach.

H. Perioperative management of patients with prior PCI undergoing unplanned surgery

1. The ideal waiting time before proceeding with noncardiac surgery should be at least
 - (a) 2 to 4 weeks for balloon angioplasty,
 - (b) 4 to 6 weeks for BMS, and
 - (c) 12 months for DES.
2. For patients who need noncardiac surgery that falls within the time frame that requires dual antiplatelet therapy and cannot be delayed, strong consideration should be given to continuation of dual antiplatelet therapy whenever possible.
3. If the risk of bleeding with dual antiplatelet therapy outweighs the benefit, serious consideration should be given to continuation of at least aspirin whenever possible. Clopidogrel should be resumed as soon as possible after surgery.
- I. It is important to recognize that **the recommended time frames for dual antiplatelet therapy are arbitrary and based on expert opinion**. These cases should be addressed individually with good communication between the cardiologist, anesthesiologist, and the surgeon. **Certain conditions might require longer dual antiplatelet therapy** (e.g., left main stenting, history of stent thrombosis, multivessel stenting, and stenting of the only remaining coronary artery or bypass graft).

Because of the lack of prospective studies as well as guidelines, there are a wide variety of potential approaches to the perioperative management of patients with stents taking dual antiplatelet therapy. The ACC/AHA/SCAI/ACS/ADA Science Advisory Panel notes the importance of 12 months of dual antiplatelet therapy after placement of a DES and educating the patient about the hazards of premature discontinuation. Therefore, management should be carried out on a case-by-case basis. Major factors that should be considered are surgical hemorrhagic risk and the thrombotic risk of the stent.

VIII. MANAGEMENT OF SPECIFIC PREOPERATIVE CONDITIONS

- #### A. Valvular heart disease.
- In general, the indications for evaluation and treatment of valvular heart disease are similar to those in the nonpreoperative setting. Symptomatic stenotic lesions are associated with increased perioperative morbidity, whereas symptomatic regurgitant valve diseases can usually be managed medically and with close monitoring perioperatively.
1. Critical **aortic stenosis** must be recognized promptly and, if symptomatic, should be managed with valve replacement or, for selected patients, valvuloplasty as a short-term bridge through noncardiac surgery.
 2. **Mitral stenosis** when mild and asymptomatic is managed medically with heart rate control. When mitral stenosis is severe and symptomatic, mitral valvuloplasty or valve replacement is considered before a high-risk operation is performed.
 3. For patients with **aortic or mitral regurgitation**, the medical regimen is optimized with diuretics and afterload reduction.
 4. Appropriate **prophylaxis for bacterial endocarditis** is administered for patients with valvular disorders according to the guidelines.
 5. Patients with **prosthetic valves who need oral anticoagulation** can usually safely undergo minimally invasive procedures such as dental work or skin biopsy if the international normalized ratio is briefly reduced to a low or

subtherapeutic range. Full anticoagulation is resumed after the procedure. For patients undergoing extensive surgical procedures with prosthetic valves, intravenous unfractionated heparin therapy is initiated. Heparin can be reserved for the following patients:

- (a) those with recent thromboembolic events (< 1 year);
- (b) those with mechanical valve in the mitral position;
- (c) those with a history of thromboembolism while not on anticoagulation
- (d) those with Bjork-Shiley or Starr-Edwards valve; and
- (e) those with three or more of the following risk factors (atrial fibrillation [AF], previous thromboembolism, hypercoagulable condition, mechanical prosthesis, and left ventricular EF < 30%).

Mechanical valves in the mitral position are usually more thrombogenic and, therefore, require a lower threshold for heparin conversion. The use of low-molecular-weight heparin may provide an alternative approach for anticoagulation, but is still controversial as valve thrombosis has been reported with its use. Oral anticoagulants are resumed as soon as possible after the procedure.

- B. Arrhythmias.** The ACC/AHA 2007 guidelines recognize **high-grade atrioventricular block, symptomatic bradycardia, symptomatic or newly recognized ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate, and symptomatic bradycardia as active cardiac conditions that require further evaluation before proceeding with noncardiac surgery.** The following points are important to remember while evaluating arrhythmias in the preoperative setting:

1. Identification of any **underlying cardiac disease, drug toxicity, or metabolic disturbances** that could be the cause of the arrhythmia is very important.
2. For symptomatic and hemodynamically significant arrhythmias, therapy should target the underlying cause and then the arrhythmia itself.
3. The indications for antiarrhythmic therapy and cardiac pacing are similar to those in nonoperative setting.
4. Frequent premature ventricular beats and asymptomatic nonsustained ventricular tachycardias are not associated with increased perioperative cardiac risk.

- C. Permanent pacemakers and implantable cardioverter-defibrillators (ICDs).** It is important to identify patients who have pacemakers or ICDs. Patients who are completely pacemaker-dependent should have their device checked within 3 to 6 months before surgery, and their device should be reprogrammed to an asynchronous mode during surgery (VOO or DOO); in certain models, a magnet can be placed over the device during surgery. Electrocautery should be used only briefly and with caution. Bipolar pacing minimizes the risk of electrocautery. After the operation, all pacemakers are interrogated to ensure that the settings are optimal and that no changes occurred during the operation or electrocautery. ICDs are programmed to off preoperatively and then reprogrammed to on after the procedure.

- D. Hypertension.** In general, patients with hypertension may be indirectly predisposed to perioperative myocardial ischemia, since CAD is more prevalent among these patients. In addition, because of the stiffness of the vascular system, they are predisposed to intraoperative hypotension; therefore, they should be **monitored closely during an operation.**

1. Patients with **mild or moderate** hypertension may undergo elective operations with continued medical therapy.
2. **Severe** hypertension (systolic blood pressure ≥ 180 mm Hg and diastolic pressure ≥ 110 mm Hg) should be controlled before the surgery. If possible, the operation is delayed until the pressure is consistently controlled. If urgent surgical intervention is needed, rapid-acting agents are used. β -Blockers are preferred, especially because they act as anti-ischemic agents as well.

3. Withdrawal of β -blockers and clonidine from patients undergoing long-term therapy with these agents **must be avoided** to prevent a rebound phenomenon.
- E. **Heart failure** is associated with increased risk of perioperative morbidity. Identification of the etiology of heart failure is very important, since the treatment **depends on the cause** and overall clinical status.
 1. Heart failure should be optimally controlled preoperatively with special attention to avoid over-diuresis, which can exacerbate postoperative hypotension.
 2. Patients **with hypertrophic cardiomyopathy** need close monitoring of volume status, heart rate, and systemic vascular resistance to avoid intraoperative hypotension and hypovolemia that can lead to exacerbation of dynamic outflow obstruction.

IX. PERIOPERATIVE MEDICAL THERAPY

- A. **β -Blockers:** Several trials and meta-analyses have examined the role of β -blockers in preventing perioperative cardiac complications. However, there remain multiple limitations in interpreting the data due to the paucity of randomized clinical trials, the lack of clear protocol for initiation and titration of β -blockers, and the lack of comparison between different agents. These limitations regarding the use of β -blockers perioperatively were acknowledged by the ACC/AHA in the latest ACC/AHA 2007 guidelines. Since the publication of these guidelines, POISE (PeriOperative ISchemic Evaluation) trial, a randomized, controlled trial of fixed higher dose, extended-release metoprolol started the day of surgery in more than 8,000 patients undergoing noncardiac surgery, prompted a 2009 ACCF/AHA focused update on the subject of perioperative β -blocker therapy. It demonstrated a reduction in primary cardiac events including cardiovascular death, MI, and cardiac arrest in those receiving perioperative β -blocker therapy. However, there was also an increased risk of stroke and total mortality in the β -blocker group suggesting that routine administration of high-dose β -blockers without dose titration may be harmful to β -blocker-naïve patients undergoing surgery. Specifically, β -blockade should continue during the intraoperative period and postoperative period to maintain a heart rate of 60 to 80 beats/min to avoid the pitfalls of this class of drug. In patients with indications for β -blockers, these agents can be continued indefinitely, and if there is no indication they should be continued for at least 7 days, and preferably 30 days after the noncardiac surgery.
 1. β -Blockers should be continued in all patients undergoing surgery who are already receiving β -blockers for any class I guideline indication (to treat angina, arrhythmias, hypertension, etc.).
 2. β -Blockers titrated to heart rate and blood pressure should be administered to all high-risk patients identified by myocardial ischemia on preoperative assessment undergoing vascular surgery.
 3. β -Blockers titrated to heart rate and blood pressure are reasonable for patients undergoing vascular or intermediate-risk surgery in whom preoperative evaluation reveals CAD.
 4. β -Blockers titrated to heart rate and blood pressure are reasonable for patients undergoing vascular or intermediate-risk surgery who have more than one clinical risk factor.
 5. The usefulness of β -blockers is uncertain for patients undergoing vascular or intermediate-risk surgery who have only one or no clinical risk factor.
 6. β -Blockers should not be administered in preoperative patients with absolute contraindications to the agents.
- B. **α_2 -Agonists** suppress the release of catecholamines and may decrease the incidence of cardiac events in patients with known CAD and at least one clinical risk factor who are undergoing noncardiac surgery.

- C. The role of **calcium antagonists** is not well defined and requires further research.
- D. **Statins.** There has been growing evidence suggesting an association between perioperative statin therapy and decreased perioperative cardiac complications. Definite indications for perioperative statin use await the results of ongoing and future clinical trials. However, it is important to note that perioperative evaluation represents an opportunity to identify patients who meet National Cholesterol Education Program criteria and impact their long-term outcome.
 - 1. Statins should be continued in patients who are already on statin therapy and undergoing noncardiac surgery.
 - 2. For patients undergoing vascular surgery, it is reasonable to be on statin therapy.
 - 3. Statins may be considered for patients with at least one clinical risk factor who are undergoing intermediate-risk surgery.

X. ANESTHETIC AGENTS AND PERIOPERATIVE HEMODYNAMIC MONITORING

- A. Several studies have evaluated the effect of **anesthetic agents and techniques** on cardiac morbidity. It appears that there is **no one best myocardial protective agent**. All inhalational agents cause depression of myocardial contractility and afterload reduction, which can lead to hypotension. Several studies have suggested that **neuroaxial anesthesia (epidural and spinal)** may reduce pulmonary and thrombotic complications compared with general anesthesia. However, its role in lowering cardiac complications remains controversial. Decisions regarding anesthetic techniques are best left to the anesthesiologist. Perioperative pain management is important because it reduces postoperative catecholamine response and cardiac stress.
- B. **Pulmonary artery catheters** are occasionally used in high-risk patients (advanced heart failure and severe CAD) who are undergoing procedures associated with significant hemodynamic stress. The ACC/AHA guidelines advise to assess the benefit versus risk when considering the use of pulmonary artery catheters. Catheter-guided volume optimization has no clear benefit perioperatively, and multicenter randomized trials have shown that pulmonary artery catheter use provides no benefit after noncardiac surgery or in the intensive care unit.

XI. POSTOPERATIVE MONITORING AND MANAGEMENT OF EVENTS

- A. **Postoperative MI.** The pathophysiology of perioperative MI is not well defined and may be different from that of nonoperative MIs. Stress, inflammation, hypercoagulability, and hypoxia may all be contributing factors. The incidence of perioperative MI ranges from 2% to 6% in general. However, up to 50% of perioperative MIs may go unrecognized. The majority of perioperative MIs occur within the first 3 days after surgery, a period when the patients are receiving narcotics that could mask the pain, some patients are still intubated and sedated, and many of the clinical signs that patients normally manifest are attributable to other causes (e.g., hypovolemia, bleeding, and pain). Nonspecific findings, such as CHF, hypotension, nausea, or ST-segment depression, may be the only clues to postoperative ischemia. The prognosis of these unrecognized MIs is nevertheless similar to that of patients experiencing a recognized MI.
 - 1. There are **no standard criteria for the diagnosis of perioperative MI in patients undergoing noncardiac surgery**.
 - 2. **Troponin** is a more specific marker for perioperative MI than creatine kinase-myocardial band, which could be falsely positive after surgery.
 - 3. **ECG and troponin** should be checked postoperatively in **patients with signs and symptoms suggestive of ischemia, but based on the current literature, routine measurement of troponin is not recommended after noncardiac surgery**.
 - 4. It is also important to rule out **other causes for positive troponin, such as pulmonary embolism**.

5. Although there is an increase in use of intraoperative **transesophageal echocardiography** to monitor myocardial ischemia through wall motion abnormalities, there is insufficient information to make firm recommendations.
 6. There are **no clear guidelines for the management of perioperative MIs. Identifying and treating correctable causes** is important (e.g., anemia and hypoxia). In general, primary PCI is preferred for **perioperative ST-elevation MI**. Although thrombolytic, antiplatelet, and anticoagulant therapies are beneficial in the treatment of non-ST-elevation MI or unstable angina in nonoperative setting, these therapies could potentially cause more harm than benefit in perioperative settings. Many drugs that are important in the long-term management of nonoperative MIs (e.g., aspirin, angiotensin-converting enzyme inhibitors, β -blockers, and statins) may not carry the same positive effect in perioperative MI patients. Large randomized clinical trials are needed to answer these questions.
 7. Nonfatal perioperative MI is an independent risk factor for cardiovascular death and nonfatal MI during the 6 months following the surgery. Therefore, close follow-up with aggressive risk-factor modification is important for these patients.
- B.** The management of **postoperative heart failure and pulmonary edema** is not much different than in nonoperative settings. ECG and troponin should be checked to rule out MI.
- C. Arrhythmias.** Perioperative arrhythmias are common, especially among elderly patients and after thoracic surgeries. For patients with arrhythmias, the metabolic profile and medications should be reviewed, and any underlying reversible conditions should be corrected, including hypoxia, fever, bleeding, pain, and infection. β -Blockers and calcium channel blockers can reduce postoperative tachyarrhythmias.
1. Most **supraventricular tachycardias (SVTs)** necessitate rate control until the underlying cause is addressed. This can be achieved using β -blockers, calcium channel blockers, or digoxin. Adenosine can be effective in terminating certain reentrant tachycardias. New-onset **AF** raises embolic risk. To avoid the increased bleeding risk with anticoagulation after surgery, restoring sinus rhythm is often a preferred strategy. Rate control is advised and if the AF persists more than 24 hours, antiarrhythmic drugs could be used. Most AF will resolve within 36 to 48 hours, but if it persists, then anticoagulation is warranted. At any time if the SVT causes hemodynamic compromise or ongoing myocardial ischemia, electrical cardioversion is the therapy of choice.
 2. Symptomatic **bradyarrhythmias** are managed with temporary pacing, and a permanent pacemaker can be implanted if and when indicated.

XII. POSTOPERATIVE MANAGEMENT. In most cases, the results of the preoperative evaluation determine whether a patient is at substantial cardiac risk. For these patients, postoperative care is dictated by the findings before the operation. In a few urgent cases, or for patients who did not undergo preoperative evaluation, postoperative evaluation and care are individualized.

- A.** After a patient has successfully undergone a procedure, the physician **assesses and manages risk factors** for coronary and peripheral atherosclerosis.
- B.** Management of risk factors, including smoking cessation, control of labile hypertension, aggressive management of hyperlipidemia, and glycemic control for patients with diabetes, is of paramount importance.
- C.** Particular attention is given to **patients who sustain perioperative MI or demonstrate perioperative ischemia** because these patients are at risk for recurrent MI or cardiac death in subsequent years. These patients should be followed closely and treated aggressively.

ACKNOWLEDGMENTS: *The author thanks Drs. Khaldoun G. Tarakji, John H. Chiu, and Vasant B. Patel for their contributions to earlier editions of this chapter.*

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Hypertensive Crisis

I. INTRODUCTION

A. Epidemiology. More than 50 million people in the United States are diagnosed with systemic hypertension, many of whom are inadequately treated. Approximately 1% of those poorly treated progress to a crisis phase, accounting for more than 50% of all cases of hypertensive crisis. Although the incidence is decreasing due to improved awareness, treatments, and public health measures, patients with untreated hypertension or suboptimal blood pressure control remain more susceptible to acute rises in blood pressure. Patients with secondary causes of hypertension are also at higher risk for hypertensive crisis. Unless promptly recognized and treated, hypertensive crisis can lead to acute central nervous system, renal and cardiovascular dysfunction, and, possibly, death. Effective and prompt antihypertensive treatment improves prognosis.

B. Definitions. Hypertensive crisis is defined as having either a **hypertensive emergency or hypertensive urgency**. According to the Joint National Committee on Detection, Evaluation and Treatment of High Blood Pressure, normal blood pressure is defined as a systolic blood pressure < 120 mm Hg and a diastolic blood pressure < 80 mm Hg. Severe hypertension is defined as a systolic blood pressure > 180 mm Hg and/or diastolic blood pressure > 120 mm Hg.

- 1. Hypertensive emergency.** Hypertensive emergency is defined as **severe hypertension with evidence of acute end-organ damage**, which can be manifested by a variety of syndromes (Table 35.1). Severe hypertension in the presence of chronic organ damage without associated acute manifestations does not constitute an emergency. Delineating hypertensive emergency from urgency is important because it implicates the need for immediate parenteral blood pressure lowering therapy in a monitored setting (typically intensive care unit [ICU]) to minimize tissue damage and long-term complications. Delay may cause irreversible organ dysfunction and death.
- 2. Hypertensive urgency.** Hypertensive urgency, on the other hand, is generally defined as **severe hypertension without acute end-organ damage**. In the absence of symptoms or acute organ dysfunction, severe hypertension can be lowered over a period of days to weeks. Patients can be treated with oral medications and usually managed as outpatients.
- 3. Pseudoemergencies.** Pseudoemergencies are acute rises in blood pressure attributed to a **physiologic trigger, causing a massive sympathetic or catecholamine surge**. These are typically seen as the result of pain, hypoxia, hypercarbia, hypoglycemia, anxiety, or a postictal state. These scenarios must be differentiated from true hypertensive crises because the management differs significantly. Treatment is directed at the underlying trigger and does not necessarily include antihypertensive medications.

TABLE 35.1 Hypertensive Emergencies**Severe hypertension (> 180/120 mm Hg) with any of the following:**

Encephalopathy
 Acute stroke, intracranial hemorrhage, head trauma
 Acute aortic dissection
 Pulmonary edema
 Myocardial ischemia and/or infarction
 After coronary artery bypass surgery
 Postoperative bleeding at vascular suture lines
 Acute renal failure and/or hematuria and proteinuria
 Retinal hemorrhages, exudates, papilledema
 Eclampsia

II. PATHOPHYSIOLOGY

A. Autoregulation. Understanding autoregulation is the cornerstone of managing hypertensive crises safely while minimizing the risk of iatrogenic complications. The kidney, brain, fundi, and heart all possess autoregulatory mechanisms that maintain blood flow at near-constant levels despite fluctuations in blood pressure. This protects these vital organs from the consequences of hypoperfusion with decrease in blood pressure and hyperperfusion with increase in blood pressure. The cardiovascular equivalent to Ohm's law in physics ($I = V/R$) is that blood flow is equal to pressure divided by resistance. Constant blood flow is maintained by parallel changes in these two parameters: pressure and resistance. The endothelial layer in these vessels controls local autoregulatory vasoconstriction when the perfusion pressure increases and vasodilation when perfusion pressure decreases. There is a range of pressures for which the autoregulatory mechanism functions normally. In normotensive patients or in those with adequate hypertension management, this range of mean arterial pressures (MAPs) is approximately between 60 and 120 mm Hg. Loss of autoregulatory control at an MAP of 120 mm Hg in patients without preexisting chronic hypertension explains why a seemingly trivial elevation in blood pressure (160/100 mm Hg) can have severe end-organ damage. Classic examples of this phenomenon occur with acute illnesses such as acute glomerulonephritis, preeclampsia, and cocaine abuse. However, in chronically hypertensive patients, either undiagnosed or inadequately controlled, the autoregulatory range is shifted to the right from arteriolar smooth muscle hypertrophy. This hypertrophy minimizes the transmission of pressure to the capillary bed, allowing tissue tolerance of higher blood pressures, but at the same time places the patient at risk for hypoperfusion if treated to normotensive pressures (Fig. 35.1). **This is the reason that blood pressure should not be reduced too quickly in chronically hypertensive patients since this will result in relative hypotension causing tissue hypoperfusion.** Gradual reduction in blood pressure allows the rightward-shifted autoregulatory curve to normalize as the arteriolar hypertrophy slowly regresses. Treatment must be tempered by the fact that **abrupt overzealous blood pressure reduction may lead to hypoperfusion and ischemia, with potential for irreversible neurologic damage.** Cerebrovascular accidents, blindness, paralysis, coma, myocardial

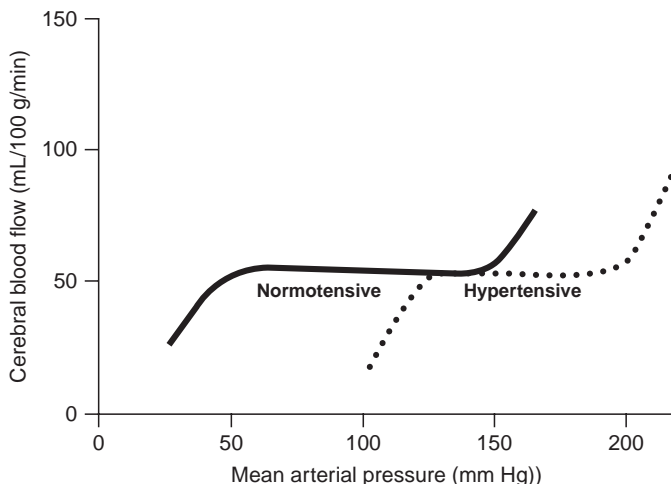


FIGURE 35.1 Autoregulatory cerebral blood flow response to changes in mean arterial pressure. Rightward shift of the autoregulation curve in chronically hypertensive patients. Adapted from Strandgaard S, Olesen J, Skinhoj, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. *BMJ*. 1973;1:507–510.

infarction (MI), and death have been reported as consequences of overaggressive blood pressure reduction.

- B. Endothelial damage.** Hypertensive emergencies are triggered by an abrupt increase in systemic vascular resistance (SVR) caused by elevated levels of circulating vasoconstrictors (e.g., norepinephrine and angiotensin II). The resultant increase in blood pressure leads to **arteriolar fibrinoid necrosis and endothelial damage**. This endothelial damage is the etiology of the loss of autoregulatory function. In addition, the necrotic fibrinoid debris causes narrowing and obliteration of the vascular lumen. Target organ dysfunction ensuing from these two processes causes further release of vasoactive substances, producing a cycle of increasing SVR, elevated systemic blood pressure, vascular injury, and tissue damage. This is the vicious cycle that propagates the hypertensive emergency.
- C. Manifestations.** The endothelial damage and escape from autoregulatory control during a hypertensive crisis leads to the classic acute end-organ complications. Because the brain is encased in a finite space in the skull, the excess blood flow results in cerebral edema and elevated intracranial pressure (ICP), leading to encephalopathy and seizures. In the kidney, the fibrinoid necrosis as well as the excess blood flow destroy glomeruli, resulting in proteinuria, hematuria, and acute renal failure. The acute injury to the fundi is manifested by exudates, hemorrhage, papilledema, and potentially blindness. The cardiovascular system can suffer from myocardial ischemia and pulmonary edema from the increased afterload state as well as aortic dissection and hemolysis from the shear stress.

III. ETIOLOGY. It is estimated that 30% to 40% of patients with a hypertensive crisis have an identifiable underlying cause compared with < 5% of those with hypertension who have not had a crisis. Evaluation for such secondary causes and precipitants is indicated in all patients with a hypertensive crisis.

TABLE 35.2 Conditions That May Precipitate a Hypertensive Crisis

Essential hypertension from undiagnosed or poorly controlled hypertension (most common)
Nonadherence to antihypertensive medication regimen
Renovascular disease
Acute, as well as chronic, renal parenchymal diseases
Acute central nervous system insults (e.g., ischemic stroke and intracranial hemorrhage)
Drug-induced (e.g., interactions, idiosyncratic reactions, exaggerated effects, and abrupt withdrawal)
Collagen vascular disease and vasculitis (classically scleroderma)
Preeclampsia
Pheochromocytoma
Obstructive sleep apnea

- A. A common scenario is that of a patient inadequately treated for chronic hypertension or one that is medically nonadherent.
- B. Risk factors for progression to hypertensive crisis include male gender, black race, low socioeconomic status, cigarette smoking or other tobacco abuse, and oral contraceptive use. Unlike primary hypertension, the incidence of which increases with age, the peak incidence of hypertensive crisis occurs among people aged 40 to 50 years.
- C. Underlying pathologic states that can precipitate hypertensive crises include renal parenchymal disease, renovascular hypertension, collagen vascular disease and scleroderma, pheochromocytoma, vasculitis, preeclampsia, and neurologic disorders (Table 35.2).
- D. A number of **medications and illicit drugs** can cause marked elevations in systemic blood pressure. The most common offenders are **cocaine**, oral contraceptives, sympathomimetic agents (e.g., diet pills and amphetamines), cold remedies (especially pseudoephedrine), nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, and monoamine oxidase inhibitors. Withdrawal from medications and illicit drugs can also precipitate severe hypertension. Examples include alcohol, benzodiazepine, and clonidine withdrawal.

IV. CLINICAL PRESENTATION

A. History

1. **Symptoms.** The history should focus on the organs that are known to suffer from end-organ damage: cardiovascular, neurologic, renal, and ocular. Cardiopulmonary symptoms include shortness of breath and chest pain. Neurologic symptoms include headache, confusion, lethargy, altered mental status, nausea, and vomiting. Oliguria and change in urine color to suggest hematuria may be the symptoms volunteered by the patient if there is renal damage. Blurred vision or change in vision suggests ocular involvement.
2. **Symptom chronology.** Among patients with severe hypertension, symptom chronology and the duration of uncontrolled blood pressure should be elicited, as this will guide the aggressiveness of blood pressure control.
3. **History of hypertension.** Most patients with hypertensive crises have an underlying history of chronic primary hypertension; however, a significant proportion have secondary forms of hypertension. Age of onset of hypertension as well as other potential clues to a secondary form of hypertension should be assessed.

4. **Contributory medication history** may include NSAIDs, oral contraceptives, erythropoietin, psychotropic agents, monoamine oxidase inhibitors, ephedrine, cyclosporine, tacrolimus, over-the-counter cold remedies, and many other medications. Withdrawal from clonidine is always a risk factor for a crisis in hypertensive patients to whom this medication has been previously prescribed. For those on antihypertensive medications it is crucial to elicit administration history, as a frequent, and potentially catastrophic, complication occurs when severe hypotension is induced by initiation of all outpatient medications in a patient with nonadherence.
5. **History of use of recreational drugs** such as **cocaine** and amphetamines, nonprescription stimulants including sympathomimetic weight loss pills, and performance-enhancing substances for athletes is important to elicit.
6. **Smoking history.** Smokers are at increased risk for progression to severe hypertension, perhaps due to endothelial dysfunction and dysfunctional autoregulation.

B. Physical findings

1. **Vital signs.** Blood pressure is measured in both upper and lower extremities to evaluate for stenosis or dissection of the aorta or great vessels. Severe hypertension is confirmed by taking two blood pressure measurements separated by 15 to 30 minutes. **No absolute level of blood pressure differentiates an emergency from an urgency. The distinction is based upon the assessment of acute end-organ damage.**
2. **Optic fundi** are examined for signs of retinopathy, including exudates, hemorrhages, or papilledema.
3. **Neurologic assessment** is performed to assess mental status and neurologic motor deficits. Patients with hypertensive encephalopathy may manifest neurologic signs of confusion or seizure activity.
4. **Cardiovascular and pulmonary systems** are examined for the presence of an S_3 , S_4 , new murmur, and/or pulmonary edema. Total volume status should be assessed, as certain treatments can cause severe hypotension in the setting of volume depletion and other medications are less effective in the setting of fluid overload.
5. **Vascular system** is examined by palpation of pulses and auscultation for bruits, especially renal bruits.

V. DIAGNOSTIC EVALUATION. If a hypertensive emergency is suspected, appropriate arrangements for ICU admission and parenteral treatment should not be delayed while waiting for the results of further tests. Chest pain, shortness of breath, headache, blurred vision, signs of altered mental status, focal neurologic deficits, retinal exudates and hemorrhages, crackles, an S_3 gallop, and pulse deficits all point toward an emergency. Diagnostic testing can be performed after treatment has been instituted.

- A. **Complete blood count and blood smear.** The presence of anemia with schistocytes should raise concerns for hemolysis and microangiopathic hemolytic anemia.
- B. **Blood chemistries** to evaluate for renal function and electrolyte levels. Hypokalemia and other electrolyte disturbances may give a clue to a secondary cause of hypertension (e.g., primary hyperaldosteronism and Cushing's syndrome).
- C. **Urinalysis** to look for proteinuria, hematuria, and casts. **Hematuria** and moderate to severe **proteinuria** are surrogate markers for glomerular damage.
- D. **Finger-stick glucose test** should be performed to exclude hypoglycemia as the cause of altered mental status in the setting of suspected hypertensive encephalopathy as well as a cause of a pseudoemergency.
- E. **Electrocardiogram** to evaluate for myocardial ischemia and chronicity of hypertension with evidence of left ventricular hypertrophy. **Cardiac markers** of ischemia (creatine kinase and troponin) should be checked but troponin is a very sensitive

marker and will commonly be slightly above the upper limit of normal in severely hypertensive patients. This, in isolation, should not be considered acute end-organ damage.

- F. **Chest radiograph** assesses heart size, can confirm auscultatory findings of pulmonary edema, and may show a widened mediastinum to suggest an aortic dissection.
- G. **Computed tomography and/or magnetic resonance imaging (MRI) of the brain** may be indicated to evaluate neurologic deficits and altered mental status, especially in the setting of suspected primary stroke, hemorrhage, or trauma.
- H. A urinary **toxicology screen** should be collected, as cocaine and other illicit drugs frequently cause severe hypertension.
- I. Prior to initiating treatment, especially in hypertensive urgencies, obtaining **renin and aldosterone** level measurements as well as serum and urine **metanephrine** samples assists with retrospective analysis for a secondary cause of hypertension. Many of the medications used to treat hypertension (β -blockers, diuretics, and angiotensin-converting enzyme [ACE] inhibitors) confound the interpretation of these tests. This diagnostic evaluation should never delay treatment of a patient presenting with hypertensive emergency.
- J. After appropriate management and resolution of the crisis, work-up for common **secondary causes of hypertension should be performed**. Renovascular hypertension is very commonly seen in these patients. In addition, primary hyperaldosteronism, coarctation of the aorta, obstructive sleep apnea, and Cushing's syndrome are frequently undiagnosed and should be investigated if the particular patient has suggestive features.

VI. THERAPY. The presence of **acute or rapidly progressive end-organ damage, and not the absolute blood pressure reading, determines whether the situation is an emergency or an urgency.** This determination dictates the type of treatment (i.e., parenteral or oral) and the setting (i.e., ICU, hospital ward, or outpatient) in which it is implemented. Management of acute hypertensive syndromes should be tailored to each patient and based on the presence, absence, and type of end-organ damage. For example, a blood pressure of 130/90 mm Hg may represent a hypertensive emergency for a patient with an aortic dissection, whereas a blood pressure of 200/120 mm Hg for a patient with asymptomatic chronic hypertension without acute end-organ dysfunction does not necessitate emergent parenteral therapy. The appropriate diagnostic evaluation and therapeutic plan are also dictated by the different variations of hypertensive crisis. For example, a pregnant woman with preeclampsia, a man with acute pulmonary edema, and an elderly patient with hypertensive encephalopathy require different diagnostic and pharmacologic strategies.

A. Hypertensive emergencies

1. **Goals of therapy** include immediate but controlled reduction of the MAP. The pharmacologic characteristics and potential toxic side effects of antihypertensive agents must be understood and anticipated.
 - a. Patients are **treated in an ICU**, where clinical status and vital signs can be constantly monitored with the aid of an intra-arterial line.
 - b. **Blood pressure is reduced in a controlled and predictable manner.** It is recommended that **blood pressure be reduced initially by no more than 25% of MAP over minutes to hours.** After the first 24 hours, further reductions should occur over days to weeks in order to allow the autoregulatory mechanisms to reset. **Exceptions include aortic dissection, postoperative bleeding, and pulmonary edema, all of which demand more aggressive blood pressure reduction to prevent catastrophic complications.**
2. **Medical therapy.** A number of parenteral antihypertensive medications are available to manage hypertensive emergencies. Characteristics of an ideal agent include rapid onset and cessation of action, a predictable dose-response curve,

TABLE 35.3 Parenteral Medications Used to Manage Hypertensive Emergencies

Drug	Dosage	Onset/duration	Indications	Side effects
Nitroprusside sodium (Nipride, Nitropress)	Infusion: 0.25–10 µg/kg/min	Immediate/3–5 min	Most emergencies	Nausea, vomiting, sweating, thiocyanate, and cyanide poisoning
Nitroglycerin (a.k.a. glyceryl trinitrate) (Nitro-Bid)	Infusion: 5–200 µg/min	Immediate/3–5 min	Myocardial ischemia, myocardial infarction, left ventricular failure	Headache, methemoglobinemia, tolerance with prolonged infusion
Labetalol (Normodyne, Trandate)	Bolus: 20 mg/5 min until desired effect (max 80 mg) Infusion: 1–2 mg/min	5–10 min/1–8 h	Most emergencies except those complicated by left ventricular failure	Heart block, orthostatic hypotension
Nicardipine (Cardene)	Infusion: 5–15 mg/h	5–10 min/1–4 h	Most emergencies except those complicated by left ventricular failure	Reflex tachycardia, headache, nausea, flushing Avoid in heart failure
Clevidipine (Cleviprex)	Bolus: 1–2 mg/h with potential doubling every 90 s for desired effect	2–4 min/5–15 min	Most emergencies except those complicated by left ventricular failure	Avoid in heart failure
Phentolamine (Regitine)	Bolus: 5–15 mg IV Infusion: 0.2–5.0 mg/min	1–2 min/3–10 min	Pheochromocytoma crisis Crisis due to catecholamine excess	Tachycardia, headache, flushing
Hydralazine (Apresoline)	Bolus: 10–20 mg IV every 30 min until desired effect achieved or side effects occur	10–20 min/3–8 h	Eclampsia	Marked hypotension, tachycardia, flushing. Contraindicated in myocardial ischemia, aortic dissection, and elevated ICP
Enalaprilat (Vasotec IV)	1.25–5 mg every 6 h	15 min/6 h	Scleroderma crisis, left ventricular failure	Marked decreases in blood pressure in high-renin states, renal failure, hyperkalemia
Fenoldopam (Corlopam)	Infusion: 0.1–0.3 µg/kg/min	< 5 min/30 min	Most emergencies, renal insufficiency	Tachycardia, headache, nausea, flushing Caution with glaucoma

ICP, intracranial pressure.

and minimal side effects. Table 35.3 lists parenteral antihypertensive agents, dosages, side-effect profiles, and specific indications.

- a. **Sodium nitroprusside is the drug of choice** for most hypertensive emergencies. This is due to its favorable hemodynamic profile, rapid onset, and rapid cessation of action. A potent, direct vascular smooth muscle relaxant, nitroprusside, decreases afterload and preload by means of dilating arterioles and increasing venous capacitance. Hemodynamic effects include a decrease in MAP, afterload, and preload; renal blood flow and renal function may improve if cardiac output improves. Although the direct cerebral vasodilation by nitroprusside may cause an adverse increase in cerebral perfusion, this is counteracted by a potent effect on MAP. Most patients with a neurologic crisis who need blood pressure control tolerate nitroprusside without a worsening of neurologic status. Unlike intravenous nitroglycerin, nitroprusside does not raise ICP or cause headaches. However, the theoretical possibility of an increase in cerebral blood flow as well as increased ICP must be kept in mind if there is further clinical deterioration despite a decrease in the MAP when using this agent.
 - (1) **Administration.** Sodium nitroprusside must be administered by constant intravenous infusion in an intensive care setting with invasive arterial blood pressure monitoring. It has a very rapid onset of action, and its effect ceases within 1 to 5 minutes of stopping the infusion.
 - (2) **Side effects.** Red blood cells and muscle cells metabolize nitroprusside to cyanide, which is converted to thiocyanate in the liver and excreted in the urine. **Thiocyanate levels rise in patients with renal insufficiency, and cyanide accumulates in patients with hepatic disease.** Signs of thiocyanate toxicity include nausea, vomiting, headache, fatigue, delirium, muscle spasms, tinnitus, and seizures. Monitoring for signs and symptoms of toxicity and maintaining thiocyanate levels at < 12 mg/dL allow safe use of nitroprusside. Thiocyanate toxicity is extremely rare in the extensive experience with nitroprusside at our institution.
- b. **Labetalol** is useful in most hypertensive crises. The main disadvantage is its relatively long duration of action. Labetalol is an α -blocker and nonselective β -blocker. When given through continuous intravenous infusion, the relative β - to α -blocking effect of labetalol is 7:1.
 - (1) The **hemodynamic effects** of labetalol include a decrease in SVR, MAP, and heart rate and a decrease or no change in cardiac output. Cardiac output is often spared because the decrease in stroke volume from the β -blockade is offset by the decrease in afterload from the α -blockade. Labetalol has little direct effect on cerebral vasculature, does not increase ICP, and is **considered by some to be the drug of choice in situations characterized by markedly elevated ICP.** Labetalol begins to lower blood pressure within 5 minutes, and its effects can last 1 to 3 hours after cessation of the infusion.
 - (2) **Contraindications.** Labetalol is contraindicated for patients with acutely decompensated heart failure, cardiogenic shock, bradycardia, second- or third-degree heart block, and severe reactive airway disease known to be exacerbated by β -blockers.
- c. **Nitroglycerin** is an important drug for managing hypertension in the setting of myocardial ischemia, acute MI, and acute cardiogenic pulmonary edema (ACPE). It is primarily a venodilator and has modest effects on afterload at high doses. The decrease in preload and afterload decreases myocardial oxygen demand. Nitroglycerin also dilates the epicardial coronary arteries, inhibits vasospasm, and favorably redistributes blood flow to the endocardium. **Nitroglycerin directly increases cerebral blood flow, raises ICP, and is not used in situations initially characterized by high ICP.**

Tachyphylaxis to nitroglycerin is well known and it is not uncommon for the blood pressure to rebound after prolonged administration. Headache is the most frequent side effect.

- d. **Fenoldopam** is a selective peripheral dopamine-1-receptor agonist approved for the management of severe hypertension. Fenoldopam is an arterial vasodilator with a rapid onset of action and a relatively short half-life when administered intravenously. It may be of particular benefit in patients with renal insufficiency, as it has been shown to improve renal perfusion. Fenoldopam may cause reflex tachycardia, which can be blunted by the concomitant use of a β -blocker. Fenoldopam is contraindicated in patients with glaucoma, because it can increase intraocular pressure. It is a potent systemic vasodilator and is used primarily by anesthesiologists to control blood pressure intraoperatively.
 - e. **Nicardipine**. As a dihydropyridine calcium channel blocker, nicardipine inhibits vascular smooth muscle contraction but has little to no activity on the heart's atrioventricular or sinus nodes. It is particularly useful in the setting of postoperative hypertensive crises and neurological scenarios, as it does not raise ICP and directly reduces cerebral ischemia. It is contraindicated in advanced heart block, acute MI, and renal failure. It is administered via a continuous intravenous infusion. **Clevidipine** is a short-acting dihydropyridine calcium channel blocker administered as a continuous infusion that does not cause reflex tachycardia. Its benefit over nicardipine is that the half-life is shorter and thus relative hypotension can be reversed quickly with cessation of the infusion.
 - f. **Enalaprilat**. This is a short-acting intravenous ACE inhibitor that lowers blood pressure abruptly. It is not widely used in hypertensive emergencies, as it can precipitate hypotension, particularly in volume-depleted patients or those with renal artery stenosis. ACE inhibitors are first-line therapy for the management of scleroderma renal crisis.
 - g. **Hydralazine**. Although very commonly administered, the role of intravenous hydralazine in hypertensive emergency should be limited to the treatment of pregnant women with preeclampsia and eclampsia. Hydralazine is a direct arterial vasodilator with no effect on venous capacitance. It crosses the uteroplacental barrier but has minimal effects on the fetus. It is usually administered in intravenous boluses of 10 to 20 mg and has a long duration of action. Hydralazine decreases SVR, induces compensatory tachycardia, and increases ICP. It can exacerbate angina and is **contraindicated in the care of patients with ongoing coronary ischemia, aortic dissection, or increased ICP**.
 - h. **Clonidine**. Clonidine should be used primarily in cases where the cause of hypertensive emergency is clonidine withdrawal.
 - i. **Oral agents**. Once the blood pressure is controlled parenterally, switching to an oral regimen that benefits the patient in the long term, based on their particular comorbidities, is recommended. In chronically hypertensive patients, this usually requires at least two antihypertensive medications. Increasing the dose of existing medications or reinitiating therapy in nonadherent patients is appropriate.
3. **Management of specific emergencies**
 - a. **Neurologic emergencies**. Patients with neurologic findings and severe hypertension present a particular challenge. Neurologic emergencies can be the result of a hypertensive emergency that will then be exacerbated by the elevated blood pressure or the result of a primary neurologic insult that causes markedly elevated blood pressures to maintain necessary perfusion. One key differentiating point is that **neurologic alterations caused by severe hypertension are reversed when blood pressure is controlled**

appropriately, whereas primary neurologic disorders typically do not improve with blood pressure control.

(1) **Hypertensive encephalopathy.** This condition occurs when cerebral edema is induced by markedly elevated blood pressures that overwhelm the autoregulatory capabilities of the brain and is characterized by headache, irritability, and an altered state of consciousness. The treatment of choice is **sodium nitroprusside or labetalol**. Agents that depress the sensorium or increase ICP (i.e., intravenous nitroglycerin) should be avoided. Mental status will classically revert to normal within hours of blood pressure reduction. **If there is no improvement despite an appropriate decrease in blood pressure, the diagnosis must be reconsidered and concern should be for a primary neurologic insult causing secondary hypertension.** During the neurologic work-up, an MRI of the brain may reveal white matter edema in the parieto-occipital regions, termed reversible posterior leukoencephalopathy syndrome. Occasionally, hypertensive encephalopathy will manifest as seizures. Along with appropriate blood pressure control, concurrent anticonvulsive therapy to terminate active seizures is appropriate; however, chronic antiepileptic therapy is not necessarily indicated since treatment of the hypertension prevents further events.

(2) **Ischemic stroke.** Although hypertension is a risk factor for ischemic strokes, the management of hypertension in the setting of an acute stroke is controversial. The elevated blood pressure is thought to be protection from hypoperfusion due to vasodilation in the peri-ischemic regions. In general, patients should not be treated unless their blood pressure > 220/120 mm Hg or they have evidence of acute end-organ damage elsewhere (e.g., aortic dissection and myocardial ischemia). In addition, in those that are eligible for thrombolytic therapy, a blood pressure < 185/110 mm Hg is required. The goal reduction is 15% in the first 24 hours. Labetalol is the preferred agent, with calcium channel blockers being acceptable alternatives.

(3) **Intracranial hemorrhage.** Intracerebral hemorrhage and subarachnoid hemorrhage (SAH) are often associated with severe hypertension. Similar to an ischemic stroke, the increased blood pressure is thought to be protective. Due to the blood within the skull, ICP increases. In order to maintain the necessary cerebral perfusion pressure (CPP) of 60 to 80 mm Hg in the setting of elevated ICP, an increase in MAP is necessary ($CPP = MAP - ICP$). Neurology consultation along with neuroimaging and intracerebral pressure monitoring is frequently used to guide blood pressure management. Nimodipine is considered the standard of care for SAH, as it prevents vasospasm commonly seen in this condition.

b. Cardiovascular emergencies.

(1) **Aortic dissection.** As opposed to most other presentations of hypertensive emergency when appropriate care requires that blood pressure be normalized slowly, in the setting of an acute aortic dissection **blood pressure must be corrected immediately**. Patients with a **type A dissection** have a mortality rate of 1% per hour in the first 48 hours unless medical therapy is instituted rapidly and the patient is referred for **emergency surgical intervention**. In the setting of an uncomplicated **type B dissection**, **antihypertensive therapy** aimed at reducing vascular resistance and shear force on the vessel wall is the treatment of choice. Aortic dissections require decreased vascular shear force by means of reducing the inotropic state of the heart and the ratio of change in ventricular pressure to the change in time (dP/dt). **This should be accomplished via**

β -blockade prior to vasodilation in order to prevent reflex tachycardia and increases in dP/dt . **Aggressive blood pressure reduction** is indicated, even for patients with normal blood pressure, because shear force and afterload must be maximally reduced to prevent extension of the dissection and/or aortic rupture. A systolic blood pressure between 100 and 110 mm Hg (or lower if tolerated) with a heart rate between 50 and 60 beats per minute is the goal. Suspect hemopericardium with tamponade or aortic rupture if hypotension is present prior to initiating therapy. **Sodium nitroprusside with an intravenous β -blocker** (metoprolol) is the treatment of choice at our institution. Continuous infusion with labetalol is sometimes used due to its combined effects on myocardial contractility as well as SVR but the fixed β -blockade to α -blockade ratio makes independent titration of blood pressure and heart rate challenging. Fenoldopam, esmolol, and diltiazem infusions are options as well.

- (2) **Acute cardiogenic pulmonary edema.** Often termed flash pulmonary edema, **ACPE due to severe hypertension** is best treated with **sodium nitroprusside or nitroglycerin**. Because of the pulmonary edema, a common reflexive action is to administer intravenous loop diuretics; however, this may have deleterious effects downstream. Accepting this seemingly paradoxical statement requires insight into the pathophysiology of pulmonary edema in this particular setting. The patients at risk for ACPE tend to be older in age with long-standing hypertension or diabetes, all of which impair diastolic function. The **acutely** elevated blood pressure results in left ventricular afterload mismatch; left ventricular end-diastolic pressure suddenly rises with concomitant elevation of the pulmonary venous pressure. On the pulmonary capillary level, increased Starling forces cause transcapillary leak and, ultimately, pulmonary edema. If the patient is euvolemic prior to the acute pressure change, then the pulmonary edema is due to maldistribution of the intravascular volume and not due to total body volume overload. Intravenous loop diuretics may have an initial beneficial venodilatory effect, but the subsequent volume depletion can cause future hemodynamic side effects. Thus, **treatment should be aimed at decreasing the acute pressure overload and afterload mismatch**, which will reverse the fluid shift in a time frame similar to the rate of decompensation. If nitroprusside or nitroglycerin infusions are not immediately available in this setting, **nitroglycerin tablets can be given sublingually** with repeated administration until goal blood pressure is achieved. Because the ACPE is often due to rapid onset of pressure overload and not due to chronically elevated blood pressure, normalization of the blood pressure in this hypertensive emergency is well tolerated without ischemic risks. It is not uncommon to see immediate relief of dyspnea and hypoxia in a patient with florid pulmonary edema once the blood pressure is lowered. β -Blockers and calcium channel blockers must be avoided in the decompensated state since the impaired inotropy and chronotropy will exacerbate the already afterload burdened ventricle.
- (3) **Myocardial ischemia.** Preload, afterload, contractility, and heart rate determine myocardial oxygen consumption. Elevated blood pressure, and thus afterload, can induce ischemia from the increased oxygen demand. In addition, the significantly elevated blood pressure can rupture stable coronary plaques, resulting in an MI. Blood pressure reduction with nitroglycerin is the treatment of choice. Nitroprusside is added if further blood pressure reduction is required. Although the optimization of cardiac parameters is likely beneficial, it must not be forgotten

that **antiplatelet and antithrombotic therapies** are the mainstays of medical management of acute coronary syndromes. **Emergent reperfusion** is indicated in ST-elevation MIs. Heparin infusion should not be started with uncontrolled systolic blood pressures (190 mm Hg or greater), as the risk of intracerebral bleeding is significant.

- (4) **Postoperative bleeding. Postoperative bleeding from vascular suture lines should be treated with immediate normalization of blood pressure, similar to an aortic dissection.** Parenteral treatment with sodium nitroprusside, nicardipine, or labetalol is preferred. **After coronary bypass grafting, nitroglycerin** is considered the initial drug of choice to maximize cardiac perfusion.

- c. **Pregnancy.** In addition to delivery of the fetus and placenta in preeclampsia, **intravenous magnesium** therapy is the treatment of choice to prevent progression to eclampsia. Labetalol or hydralazine, combined with a β -blocker to prevent reflex tachycardia, can be used safely in pregnancy. ACE inhibitors and angiotensin receptor antagonists are contraindicated.
- d. **Pheochromocytoma. Phentolamine** is an intravenous α -adrenergic blocker useful in cases of pheochromocytoma as it is effective in cases of catecholamine excess. β -Blockers should never be used in isolation because they can cause a paradoxical increase in blood pressure due to the effects of unopposed α -receptor stimulation from circulating catecholamines.

B. Hypertensive urgencies. Most patients diagnosed with hypertensive urgency actually have chronically severe hypertension and **are not in any immediate danger of progressing to hypertensive emergency**. They are often people with chronic hypertension who are suboptimally treated or nonadherent. As previously mentioned, the key to distinguishing hypertensive emergency from urgency is to assess whether there is evidence of acute end-organ damage.

1. Goal of therapy

- a. Hypertensive urgencies can often be managed with **oral medication without admission to the hospital**. End-organ damage is not imminent, and blood pressure can be lowered modestly over a period of hours as long as adequate follow-up care is ensured. **The greatest danger lies in overtreating these patients and inciting hypotensive complications.** However, even in the absence of acute end-organ dysfunction, hospital admission should be considered for patients with a diastolic blood pressure > 140 mm Hg, those with a high risk of cardiovascular complications (known coronary disease or previous stroke), or those with uncertain outpatient follow-up.
- b. Since hypertensive urgencies can have significant morbidity if treated aggressively, lower initial doses of antihypertensive medications are used to treat patients with known cerebrovascular disease or coronary artery disease or who are volume depleted. These patients tend to have exaggerated responses to drug therapy. In addition, they are also especially vulnerable to the effects of hypotension. Monitoring for 4 to 6 hours is necessary to judge treatment effect and to look for complications. Urgent follow-up care is mandatory within 24 to 48 hours. The outpatient goal is to normalize the blood pressure over the next 2 or 3 months.

- 2. **Drug therapy.** In adherent patients already prescribed with antihypertensive medications, increasing the dose of a current medication is usually sufficient. If initiation of a new agent is required, the choice should be a medication that benefits the patient in the long-term; therefore, underlying comorbidities should be taken into account. For example, ACE inhibitors would be best for those with diabetes, chronic kidney disease, or systolic dysfunction, and β -blockers for those known to have coronary artery disease or atrial fibrillation. Although considered a first-line agent for chronic hypertension, diuretics tend to have a

poor response in severe hypertension when given as a monotherapy. However, a long-acting dihydropyridine calcium channel blocker, β -blocker, or ACE inhibitor can be started in isolation. The medications commonly used for hypertensive urgencies include captopril, long-acting nifedipine, and oral labetalol, although many other adequate choices exist.

- a. **Captopril.** Considered by some to be the drug of choice, captopril is a **fast-est-acting oral ACE inhibitor**. At small doses, it rarely causes marked hypotension, although this potential exists in patients who are markedly volume depleted or who have renal artery stenosis. Captopril begins to work within 15 to 30 minutes of ingestion and the duration of activity is 4 to 6 hours. An initial dose of 6.25 mg should be given and if hypotension does not occur within 1 to 2 hours, the patient will tolerate doses of 12.5 to 25 mg three times daily.
- b. **Nifedipine.** *The short-acting and sublingual forms of nifedipine should not be used, as profound hypotension is easily precipitated.* The long-acting form is a potent antihypertensive medication and should be initiated at 30 mg daily with uptitration as an outpatient. The onset of action is not as quick as labetalol or captopril but the daily dosing is favorable for adherence.
- c. **Labetalol.** A combined α -blocker and β -blocker, labetalol, taken orally has a relative β -blocking to α -blocking effect of approximately 3:1. Dosage begins at 100 mg (taken orally twice daily) and is titrated to the desired response. The onset of action is 30 minutes to 2 hours after administration; the duration of action is 8 to 12 hours.

VII. PROGNOSIS. The prognosis of a patient with an untreated hypertensive crisis is poor. Before the introduction of effective antihypertensive agents, 1-year mortality exceeded 80% and 5-year mortality was approximately 99%. In the modern era of effective antihypertensive medications, 10-year survival has improved to 70%. Therefore, appropriate recognition of these clinical syndromes coupled with the treatment of blood pressure in a safe and controlled manner is paramount to significantly improving outcomes for these once mortal conditions.

ACKNOWLEDGMENTS: *The author thanks Drs. John H. Chiu, Harpreet Bhalla, and Daniel Cantillon for their contributions to earlier editions of this chapter.*

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Evaluation of Chest Pain in the Emergency Department

- I. **INTRODUCTION.** Chest pain is one of the most common problems evaluated in the emergency department (ED).
 - A. Each year, approximately 5 million persons who arrive at an ED with chest pain are admitted to the hospital, mainly to an intensive care unit; 1.2 million of these patients are ultimately diagnosed with acute myocardial infarction (AMI). However, **2% to 4% of persons who arrive with chest discomfort and AMI are inappropriately discharged** to home. This error in diagnosing myocardial infarction (MI) is dangerous and costly. **Early recognition and treatment** are also important because time to treatment is the single most important factor in the management of ST-elevation MI.
 - B. **Rapid evaluation and risk stratification** of patients with chest pain are essential to identify life-threatening conditions and improve outcomes. Emergency treatment is initiated in the ED to minimize permanent myocardial damage and improve survival, especially in patients with MI. **The goal of treatment in ST-elevation MI** is to achieve reperfusion as soon as possible, either by primary percutaneous coronary intervention or by thrombolytic therapy. **Conversely, in patients with non-ST-elevation acute coronary syndrome (ACS), maintaining antegrade flow in the coronaries with prevention of distal embolization is important.** The Thrombolysis in Myocardial Infarction (TIMI) risk model is a validated mechanism to determine prognosis and guide therapy in patients with ACS. The model consists of seven variables, with one point for each variable: age > 65 years, three or more risk factors for heart disease, known coronary stenosis, multiple anginal episodes in the last 24 hours, use of aspirin in the last week, electrocardiographic changes, and elevated cardiac biomarkers (Table 36.1). **High-risk patients** are typically admitted to a coronary care unit for management with antiplatelet and antithrombotic therapies. Urgent (within hours) cardiac catheterization and appropriate revascularization are recommended in these patients. **Intermediate-risk angina patients** are directed to a monitored telemetry unit and undergo further risk stratification such as stress testing and assessment of left ventricular function with possible cardiac catheterization. **The lowest risk patients** can be observed in a chest pain unit or discharged directly to home, depending on the clinical situation.
 - C. **Assessment** of chest pain in ED involves careful patient **history, physical examination, and 12-lead electrocardiogram (ECG)**. Functional stress tests can supply additional data, but the data are not immediately available, and triage decisions are often made without them. With clinical history, physical examination, and initial ECG, 92% to 98% of cases of AMI and approximately 90% of cases of unstable angina can be identified.

TABLE 36.1 Rate of Complications in Non–ST-Segment ACS Based on TIMI Risk Score

# risk factors	0–1	1	3	4	6	6–7
N patients	85	339	627	573	267	66
% total patients	4.3	17.3	32	29.3	13.6	3.4
Rate of composite endpoint	4.7%	8.3%	13.2%	19.9%	26.2%	40.9%

TIMI, Thrombolysis in Myocardial Infarction; ACS, acute coronary syndrome; N, number.

Composite endpoint: Incidence of all-cause mortality; MI, repeat revascularization at 14 d.

Based on data from Antman EM, Cohen M, Bernink PJ, et al. TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA*. 2000;284:835-842.

II. CLINICAL PRESENTATION

A. History

1. **Chest pain.** The initial history should accurately characterize the location and duration of the patient's discomfort, associated symptoms, and aggravating and alleviating factors (Table 36.2). Most patients with ischemic chest pain describe it as substernal pressure, squeezing feeling, or a sensation of suffocation. Some patients describe it as aching, burning, or tightness. The pain may radiate to the shoulder, neck, jaw, left or right arm, and the fingertips. Occasionally, the pain may be predominantly epigastric or interscapular.
2. **Atypical presentations.** Dyspnea is often associated with chest pain during an MI. **Dyspnea** may also be the only major presenting symptom in about 10% of patients with MI. Other atypical presentations include fatigue, syncope, altered sensorium, stroke, nausea or vomiting, and lethargy. **Atypical presentations of AMI are more common in the elderly, in patients with diabetes, and in women.**
3. **Risk factors.** Although several clinical factors have been associated with an increased risk of cardiovascular disease, only the **age** of patient, **history of coronary artery disease**, and **male** sex are predictive of ACS among patients with chest pain. In some studies, diabetes and family history have been associated with ACS, but the overall power of these risk factors in predicting an ischemic event is low. The **absence of risk factors cannot be used to exclude cardiac ischemia.**

B. Physical examination

1. The physical examination helps to identify **signs of left ventricular dysfunction and occult valvular heart disease**. The presence of a third heart sound (S₃ gallop), rales, sinus tachycardia, hypotension, and increased jugular venous distention is associated with adverse outcome. The presence of these signs and symptoms indicates cardiac origin of the chest pain. A thorough physical examination also helps identify the cause of nonischemic chest pain. Chest wall tenderness, skin lesions, and pleural or pericardial rub can be useful in this regard.

TABLE 36.2 Differentiating Cardiac from Noncardiac Chest Pain

Favoring ischemic origin	Favoring nonischemic origin
Character of pain	
Squeezing	Sharp, knifelike
Burning	Stabbing
Heaviness	Aggravated by respiration
Location of pain	
Substernal	Left submammary area
Across mid-thorax	Left hemithorax
Radiation to the arms, shoulders, neck, head, forearms, interscapular region	Discomfort localized with one finger
Associated with nausea, vomiting, diaphoresis	Back pain that suggests aortic dissection
Factors provoking pain	
Exercise	Pain after completion of exercise
Excitement	Pain relieved by exercise
Stress	Provoked by a specific body motion
Cold weather	
Duration of chest pain	
Minutes	Seconds
	Hours without evidence of myocardial damage

From Selzer A. *Principles and Practice of Clinical Cardiology*. 2nd ed. Philadelphia, PA: WB Saunders; 1983:17, with permission.

2. **Response to treatment is not reliable** in unraveling the cause of chest pain. **Pain relief after administration of nitroglycerin does not necessarily point to MI or unstable angina, as other etiologies for chest pain are relieved with nitroglycerin.**

III. DIAGNOSTIC TESTING

- A. The **ECG** is integral to the evaluation of chest pain and has important diagnostic and prognostic value. It is even more important in the evaluation of persons with diabetes and elderly persons who tend to have atypical symptoms.
 1. Almost 50% of patients with MI have a normal or nondiagnostic ECG on presentation to the ED. **Sensitivity** depends on a number of factors, including the time from symptom onset, coronary distribution of ischemia, baseline ECG abnormalities, and patient characteristics. Electrocardiographic findings should normalize rapidly after resolution of chest pain. The electrocardiographic findings of a patient who does not have active chest pain are difficult to interpret.

- Circumflex distribution ischemia is notoriously silent on an ECG, as the posterolateral wall is underrepresented on a conventional 12-lead ECG.**
2. Among patients with the ischemic type of chest discomfort, ST-segment elevation on an ECG has a specificity of approximately 90% and a sensitivity of approximately 50% for the diagnosis of AMI. Specificity decreases to 82% and sensitivity increases to 69% when ST-segment elevation or depression, Q waves, or left bundle branch block (LBBB) is used to define abnormal electrocardiographic findings.
 3. The ECG can be used to identify a population of patients at low risk for MI. A normal ECG indicates < 3% risk for MI and < 6% risk for death in the following year. However, approximately one-third of patients with unstable angina may have a normal or equivocal ECG. **The ECG cannot be used alone to exclude ACS.**
 4. Preexisting abnormalities, including left ventricular hypertrophy, LBBB, Q waves, preexcitation, and paced rhythms, make interpretation of the ECG difficult. Comparison of the initial ECG with a prior tracing is often helpful in this setting. Whether new or old, the presence of **LBBB is an adverse prognostic finding**. New LBBB suggests left anterior descending coronary artery ischemia or infarct. Preexisting LBBB alone defines a group of patients at high risk for cardiac morbidity and mortality. Although LBBB complicates the electrocardiographic diagnosis of AMI, criteria have been proposed for ascertaining whether a patient has AMI and LBBB from the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO I) database.
- B. Biochemical markers** of myocardial necrosis are used in conjunction with the clinical history and ECG to confirm the diagnosis of MI. Biochemical markers include cardiac **troponins, creatine kinase-myocardial band (CK-MB) isoenzyme, and myoglobin**. These markers, especially troponins, are sensitive and specific for myocardial injury and can provide important prognostic information.
1. **Serial blood samples** are collected over a 24-hour period to measure a temporal rise and fall for the diagnosis of MI. All biochemical markers follow a predictable pattern of release after the onset of myocardial injury.
 2. An **ideal serum marker** is specific to myocardium, highly sensitive, and quantitative; the serum concentration is proportional to the amount of myocardial tissue injured. Furthermore, the levels have to increase rapidly to allow early diagnosis. None of the available markers are optimal for the diagnosis of ACS. In most cases, the combination of serial measurement of markers and interpretation of clinical data such as ischemic symptoms and ECG changes leads to the accurate diagnosis of ACS.
 3. Enzymes such as aspartate aminotransferase, lactate dehydrogenase, and total CK are released from dying myocytes but are relatively nonspecific for cardiac tissue.
 - a. **CK-MB is released into the circulation after myocardial cell death.** There is some evidence in animal models that CK-MB can be released with reversible myocardial injury. However, this has not been shown in humans.
 - Most studies have confirmed that serial measurement of CK-MB for the diagnosis of AMI has a sensitivity of approximately 92% with a specificity of 98%. The initial level of CK-MB, however, does not carry equal statistical weight and does not have sufficient negative predictive value to exclude MI when used in isolation. The CK-MB level can be increased with normal or minimally elevated total CK levels; however, the significance of this finding is debatable.
 - b. **Myoglobin** is a small heme protein that is not specific to cardiac tissue. The use of myoglobin as a marker of myocardial necrosis does not carry the

specificity of CK-MB measurement. **The advantage of myoglobin as a marker lies in its release kinetics.** Myoglobin is released rapidly after myocardial injury, and serum levels are detectable within 1 to 2 hours of the onset of symptoms. Peak serum levels are reached within 4 to 5 hours after MI. Within 1 to 3 hours of MI, serum myoglobin determination has a sensitivity of 62% to 100% in the detection of myocardial damage. Because of its short half-life, measurement of myoglobin may not help confirm the diagnosis for patients who seek treatment late after symptom onset. The specificity is low when there is a substantial release of skeletal muscle myoglobin and in the setting of renal failure.

c. Troponins

- Cardiac troponins are **proteins that regulate the calcium-dependent interactions between actin and myosin.** This interaction results in myocyte contraction and relaxation. **Troponin T** is a myofibrillary protein and is a constituent of the contractile apparatus of cardiac muscle. Cardiac troponins, like CK-MB, can be found in the serum soon after injury, but concentrations remain elevated for as long as 2 weeks. Cardiac troponin T and troponin I are useful in the diagnosis of ACS and have been shown to be very sensitive and specific markers of myocardial cell injury.
- A large, prospective analysis from the Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO IIa) trial has provided important data on the **value of cardiac troponins for diagnosis and risk assessment.**

- (i) Among patients who present within 12 hours of the onset of myocardial ischemia, elevated levels of **troponin T** (> 0.1 mg/mL) are associated with significantly higher mortality within 30 days. This is true for all ECG subgroups examined, including those with ST depression, ST elevation, T-wave inversion, LBBB, and paced rhythms. A quantitative relation has also been demonstrated between levels of cardiac troponin T and long-term clinical outcome.
- (ii) **Troponin I** also has similar prognostic value. Among patients with unstable angina and non-Q-wave MI, elevated cardiac troponin I levels (> 0.4 ng/mL) are associated with significantly higher mortality.
- (iii) **Bedside tests** for cardiac-specific troponins are **highly sensitive** for the early detection of myocardial cell injury in ACS. Qualitative and quantitative point-of-care tests for troponin T and troponin I are fast, yielding results that are reliable and accurate within a few minutes. **Negative test results have been associated with low risk** and allow rapid and safe discharge from the ED of patients with an episode of acute chest pain, as long as these tests are done at least 8 hours after the onset of chest pain.

- #### d. Novel biomarkers. B-type natriuretic peptide and C-reactive protein (CRP)
- are predictive of risk in patients with ACS. Measuring these markers in combination with troponin or CK-MB may improve the short- and long-term risk stratification of ACS patients. **Plasma myeloperoxidase** levels are elevated in persons with angiographically documented coronary disease and within culprit lesions prone to plaque rupture. Recent studies have shown that elevated myeloperoxidase levels predict cardiac risk in patients presenting to the ED with chest pain, independently of the level of CRP, troponin T, and other markers of inflammation. However, these novel biomarkers have yet to become incorporated into clinical practice guidelines for chest pain or ACS management.

- #### C. Imaging studies.
- Although clinical history, initial electrocardiographic findings, and biochemical markers have been combined to diagnose ACS with high sensitivity

and specificity, atypical presentations and equivocal electrocardiographic findings can make diagnosis challenging. Investigations aimed at overcoming these problems have focused on myocardial perfusion and functional imaging.

1. Echocardiography. Two-dimensional echocardiography provides valuable diagnostic data on ventricular function and regional wall motion abnormalities.

- a. Myocardial ischemia can cause abnormal segmental function of the myocardium manifested as impaired relaxation, hypokinesis, akinesis, or dyskinesia.
- b. Although echocardiography alone has moderate sensitivity in the diagnosis of MI, it may be a useful adjunctive test, especially after reperfusion therapy. Echocardiography serves an important role in risk stratification after MI through assessment of left ventricular function.
- c. Normal findings at echocardiography cannot be used reliably to rule out myocardial ischemia.
- d. Echocardiography can be crucial in the evaluation of complications of MI, such as ruptured papillary muscle, free wall rupture, or ventricular septal defect.

2. Radionuclide perfusion imaging is useful to quantify myocardium at risk. It is rarely used for the diagnosis of ACS because of poor accessibility and cost.

- a. **Thallium 201 scintigraphy** has been used to detect the areas of reduced or absent perfusion in AMI. Areas of myocardium with a negative scintigraphic image, indicating decreased myocardial uptake, can be demonstrated in ischemic or infarcted myocardium within 6 hours of symptom onset. The diagnostic utility of such imaging is limited by the so-called moment-in-time problem; perfusion defects may represent acutely ischemic myocardium or preexisting areas of scar tissue. Thallium 201 imaging has relatively poor specificity in women because of difficulties in distinguishing between breast attenuation and perfusion defects caused by coronary artery disease.

- b. **Technetium 99m sestamibi tomographic imaging** has the advantage that it does not redistribute after initial injection. This type of imaging allows definition of an initial ischemic zone that can be studied even after reperfusion. Technetium-derived image quality is also superior to that of thallium and allows quantification of regional and global ventricular function by gated image acquisition. Perfusion imaging with technetium 99m appears to have a sensitivity equivalent to that of thallium 201 imaging in defining myocardium at risk.

3. Computed tomography (CT). Recently, several studies have evaluated the role of multislice detector coronary CT angiogram in patients presenting to the ED with chest pain. The greatest promise of coronary CT angiogram appears to be in low-risk patients with chest pain, in whom absence of coronary artery disease has been shown to have a very high negative predictive value for subsequent diagnosis of ACS and very low rate of major adverse cardiovascular events during follow-up. The main limitation of this technology lies in the inability to determine the physiologic significance of coronary lesions of intermediate severity. Multislice detector CT has also been studied as a tool that can simultaneously assess for ACS, aortic dissection, and pulmonary embolism (PE). This approach appears promising; however, its use in the ED cannot be advocated until its clinical utility has been validated.

D. Early exercise stress testing. In general, exercise stress testing can be safely performed to further risk-stratify patients who are considered to be at a low clinical risk for MI. Studies have shown that this approach is safe in patients who have a normal or nondiagnostic ECG and negative biochemical markers for myocardial necrosis assessed within 6 to 12 hours of presentation to the ED.

IV. DIFFERENTIAL DIAGNOSIS. Differentiating ischemic from nonischemic causes of chest pain can be difficult (Table 36.3). It has been estimated that more than 50% of patients

TABLE 36.3 Differential Diagnosis of the Causes of Acute Chest Pain

Cardiac	Aortic	Pulmonary	Gastrointestinal	Miscellaneous
Acute coronary syndrome	Aortic dissection	Pulmonary embolus	Esophageal spasm/reflux	Costochondritis
Coronary spasm	Penetrating aortic ulcer	Pneumothorax	Esophagitis	Cervical spondylosis and other compression neuropathies
Syndrome X, microvascular disease	Aortic aneurysm	Pneumonia/pleuritis	Esophageal rupture	Herpes zoster
Myopericarditis				Panic disorder
Aortic stenosis				Anxiety
Hypertrophic cardiomyopathy				

initially admitted to the hospital with a diagnosis of unstable angina are later discharged with a noncardiac diagnosis. Given that there is symptom overlap among a number of clinical entities, in most diagnostic strategies, it is assumed that **chest pain is cardiac in origin until proven otherwise**. It is important to understand the clinical characteristics that represent the leading noncardiac causes of chest pain. Life-threatening causes of chest pain that can be confused with ACS include aortic dissection, pericarditis with cardiac tamponade, and pulmonary embolus.

A. Pericarditis (see Chapter 40) is often accompanied by substernal chest pain, but the **pain** is more likely to be pleuritic in character and aggravated by recumbency, deep inspiration, and swallowing. **Physical examination** may reveal a three-component pericardial friction rub. The **ECG** often reveals ST elevation in multiple leads without reciprocal changes, whereas PR-segment depression in leads other than aVR and V₁ is a more specific sign of pericarditis. It is important to recognize that **pericarditis may be a late presentation of MI**. Cardiac tamponade is characterized by hypotension, elevated jugular venous pressure, and muffled heart sounds (Beck's triad). In addition, the presence of pulsus paradoxus, defined as an abnormally large (> 10 mm Hg) decline in systolic blood pressure during inhalation, is a very helpful sign in cardiac tamponade and reflects exaggerated ventricular interdependence, the key pathophysiologic mechanism in this life-threatening condition. Prompt bedside echocardiography wherever possible is very useful in confirmation of the diagnosis as well as guidance for percutaneous pericardiocentesis.

B. Aortic dissection (see Chapter 26) requires **urgent** diagnosis because early surgical intervention reduces the high short-term mortality rate. The **chest pain** of aortic dissection is typically described as sudden, severe, and tearing pain that radiates to the back and interscapular areas, which is most intense at onset. **Examination** may reveal a difference in right and left arm blood pressures, pulse deficits, and focal neurologic deficits. Aortic dissection may also involve the aortic valve or coronary ostia. The latter may be associated with the diastolic murmur of aortic insufficiency, myocardial ischemia, and ST-segment elevation on **ECG**. Diagnosis is primarily made by transesophageal echocardiography, multislice contrast-enhanced CT, or magnetic resonance imaging. All these imaging modalities have high sensitivity and specificity in the diagnosis of acute aortic dissection. The preferred initial diagnostic imaging

modality should be based on availability, local expertise, clinical stability, and renal function. At our institution, CT is the initial test of choice in most cases of suspected acute aortic dissection.

- C. Pulmonary embolism** is potentially life threatening and can be associated with chest pain. The **chest pain** of PE is typically pleuritic in character and is associated with dyspnea and tachypnea. There is often a **history** of recent surgical intervention, malignant disease, or immobility. The cardinal **clinical findings** include hypoxia and tachycardia. An **ECG** may demonstrate right-axis deviation, right bundle branch block, or occasionally the classic $S_1Q_3T_3$ pattern. In patients with low or moderate pretest probability of PE, a D-dimer level < 500 ng/mL by qualitative enzyme-linked immunosorbent assay or semiquantitative latex agglutination excludes PE with a very high negative predictive value. Spiral CT with contrast (CT pulmonary angiography) is the main imaging modality for diagnosing acute PE with very high specificity. However, when imaging results are inconsistent with clinical suspicion, additional testing in the form of V/Q scan or lower extremity ultrasonography may be necessary.

- V. CONCLUSIONS.** The ED is where life-saving therapy is initiated in patients with ACSs. It is important to rapidly and accurately risk-stratify patients with suspected ACS. Many patients will present with noncardiac conditions for chest pain, some of which are life threatening. It is important for the ED practitioner to have a working diagnosis of the varied causes of chest pain. There is a spectrum of ACSs, which ranges from high risk to low risk. The highest risk patients require emergent reperfusion therapy, whereas lower risk patients can undergo urgent invasive therapy or further risk stratification. Such an understanding can help direct patient care most appropriately and improve important outcomes, including survival.

ACKNOWLEDGMENTS: *The authors thank Drs. Jason B. Wischmeyer, Anthony Bavy, and Michael Yen for contributions to this chapter.*

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CHAPTER

37

Imran N. Ahmad

Cardiac Trauma

I. INTRODUCTION. Trauma represents the leading cause of death in males younger than 40 years in the United States. Cardiothoracic injuries are a primary or contributing factor in up to 75% of all traumatic deaths. Cardiac trauma occurs most commonly in the setting of motor vehicle accidents, interpersonal violence, cardiopulmonary resuscitation (CPR), falls from great heights, as well as sporting and industrial accidents. **Cardiac trauma can be easily overlooked in the presence of distracting injuries, as it can occur in the absence of chest pain or visible wounds.** Emergency department physicians lead the initial management, while contemporary trauma teams are typically led by surgical subspecialists. However, cardiologists play an important consultative role in the diagnosis and management of cardiac trauma.

- A.** Cardiac trauma is divided into **blunt trauma** (i.e., motor vehicle accidents and falls) and **penetrating trauma** (i.e., primarily, knife and gunshot wounds).
- B.** As many as 50% of people with cardiac injuries die in the field, but advances in diagnostic testing and surgical techniques have improved the prognosis of patients who reach emergency centers alive. Definitive management requires rapid mobilization of the surgical team and transport to the operating room.
- C.** Initial attention is focused on the airway, breathing, and circulation, and the primary survey is performed according to the published Advanced Trauma Life Support (ATLS) guidelines. The cardiac physical examination should assess vital signs, peripheral pulses, murmurs, signs of heart failure, distended neck veins, and the presence of pulsus paradoxus. Routine laboratory evaluation should include cardiac

biomarkers, and a portable chest radiograph should be performed rapidly. **Trans-thoracic echocardiography (TTE) at the bedside is the preferred modality for the initial assessment of cardiac trauma.** Focused Assessment with Sonography for Trauma is a widely applied technique using bedside ultrasound to rapidly assess blunt trauma at multiple body sites, including the heart. An electrocardiogram (ECG) is indicated to evaluate for suspected coronary dissection or traumatic coronary thrombosis. The role for cardiac computerized tomography (CT) using intravenous contrast is expanding, and it remains the diagnostic study of choice to evaluate suspected trauma and/or dissection of the aorta and great vessels, along with transesophageal echocardiography (TEE).

II. BLUNT TRAUMA

- A. Blunt cardiac trauma generally occurs in the setting of motor vehicle accidents, but it may also be related to falls, blows from blunt objects, or CPR.
- B. Blunt trauma may injure the **pericardium, myocardium, valves or subvalvular apparatus, coronary arteries,** or the **great vessels.** The clinical presentation is generally one of **tamponade** or **hemorrhage,** depending on whether the pericardium is intact. Although hypotension and tachycardia are seen in both scenarios, tamponade is suggested by elevated neck veins, muffled heart sounds, and pulsus paradoxus and is easily confirmed by a bedside echocardiogram. A new murmur coupled with signs of heart failure should raise clinical suspicion for injury to the valves or subvalvular apparatus.
 1. **Pericardium.** Increased shear forces during blunt trauma may lead to lacerations or tears in the pericardium. Clinically, the patient may experience pleuritic chest pain, and an ECG may reveal the typical findings of pericarditis. Management is with analgesics, although late cases of constriction occasionally develop after traumatic injury to the pericardium.
 2. **Myocardium**
 - a. **Myocardial rupture.** The myocardium can be injured by several mechanisms in sudden deceleration injuries. Compression between the sternum and the spinal column, as well as sudden overdistention with blood after abdominal injuries, may lead to myocardial rupture. The thin walls and large diameter of the right atrium predispose it to rupture, and **more than 50% of cases of cardiac rupture involve the right atrium.** The left atrium may be involved in as many as 25% of cases, with the remainder involving the thicker walled right and left ventricles. Most victims die immediately, but some series suggest that survival may approach 50% if patients arrive with intact vital signs. Management requires prompt thoracotomy and definitive surgical repair. Emergency pericardiocentesis is relatively contraindicated, as it can lead to reaccumulation and arrest, and is generally only considered as a desperate measure in an arresting patient when trained personnel are unavailable to perform a thoracotomy.
 - b. **Myocardial contusion.** Blunt chest wall trauma may lead to focal injury and necrosis of cardiac myocytes, known as myocardial contusion. Definitive diagnosis is based on histology, and, therefore, the true incidence and clinical significance of myocardial contusion remain controversial. Patients may complain of precordial pain, but symptoms are usually difficult to interpret in the setting of chest wall trauma and associated injuries. A number of studies have investigated the use of ECG, cardiac enzymes, and TTE in diagnosing myocardial contusion, but none of these tests has been found to be sensitive or specific for the diagnosis. The ECG may be normal or may show nonspecific ST-T wave changes or findings consistent with pericarditis. Elevations in serum troponin levels and creatine kinase-myocardial band (CK-MB) isoenzymes are observed in some patients, but CK-MB may be masked by skeletal muscle CK-MM release, especially when total CK > 20,000 U/L.

TTE may reveal a small effusion or focal wall motion abnormalities. Patients with contusion are thought to be at increased risk for arrhythmic death during the recovery period, as the injured, inflamed myocardium behaves much like scar tissue as a substrate for slowed conduction and unidirectional block in the development of reentry cycles. However, findings on ECG, TTE, or laboratory tests are insensitive in predicting outcomes. From a practical standpoint, the diagnosis of cardiac contusion does not generally alter management, as treatment is mostly supportive care, observation, and analgesia. However, making the diagnosis should alert physicians to the potential for arrhythmias. Most centers perform a baseline ECG and monitor patients with blunt chest wall trauma for at least 12 hours before discharge.

3. **Valvular insufficiency.** Injury to cardiac valves, papillary muscles, or chordae tendineae during blunt cardiac trauma may lead to acute valvular regurgitation. A review of 546 autopsies after blunt trauma suggested that valvular injury may occur in as many as 9% of cases, with a slight increase in frequency in patients with preexisting valvular heart disease. The **aortic valve is most commonly involved**, followed in decreasing frequency by the mitral and tricuspid valves. A new murmur, hypotension, and fulminant pulmonary edema should suggest the diagnosis. The differential diagnosis of a new holosystolic murmur (occasionally with a new right bundle branch block or right-axis deviation on the ECG) should also include a traumatic ventricular septal defect. An emergency trans-thoracic echocardiogram and rapid transport to the operating room are generally required. Acute tricuspid regurgitation is generally well tolerated with lower extremity edema and fatigue as the presenting symptoms, although it occurs relatively rarely.
4. **Coronary arteries.** Blunt trauma occasionally leads to **thrombosis** or **dissection** of a coronary artery and subsequent myocardial infarction. In general, the prognosis after a traumatic myocardial infarction is better than that of the usual acute coronary syndrome because patients tend to be younger and have less atherosclerotic burden and less comorbidity. Nevertheless, patients with infarctions related to trauma are at risk for all the mechanical complications associated with atherosclerotic disease, such as left ventricular aneurysm or pseudoaneurysm formation, ischemic mitral regurgitation, and ventricular septal defect. In rare cases, blunt trauma contributes to the formation of an arteriovenous fistula between the coronary artery and another structure, such as the coronary sinus, great cardiac vein, right atrium, or right ventricle. Clinically, the patient may have a loud, widely radiating murmur, and ligation of the coronary artery or bypass surgery may be necessary.
5. **Commotio cordis.** Case reports of sudden cardiac death in children and adolescents after relatively low-impact chest wall trauma (most commonly, a baseball or hockey puck striking the chest) have received significant media attention in the past. The mechanism is unclear, but it appears that a blow to the chest during an electrically vulnerable period of cardiac repolarization may induce ventricular tachycardia or ventricular fibrillation. Victims have been surprisingly refractory to cardiac defibrillation, and few of them survive. Autopsy reports consistently show no evidence of underlying structural heart disease.
6. **Great vessels.** The aorta may also be injured in motor vehicle accidents and falls when sudden deceleration leads to tears or disruption of the vessel. Not surprisingly, most patients with aortic rupture die immediately, but 10% to 20% may reach emergency centers alive if the bleeding is limited by clot or by the pleura. Aortic rupture typically occurs at the proximal portion of the descending aorta, where the aorta is tethered against the spine by intercostal arteries and the ligamentum arteriosum. Patients frequently present with chest or back pain and hypotension, but a high index of suspicion is often needed to make the diagnosis. Increased pulse pressure in the upper extremities and diminished pulse pressure in the lower

extremities may be found on examination. The chest radiograph may reveal a widened mediastinum, large left pleural effusion, loss of the aortic knob contour, or deviation of the esophagus to the right. A normal chest radiograph, seen in as many as 25% of patients, does not rule out acute aortic pathology.

CT scan with intravenous contrast is generally the first-line imaging modality for the diagnosis of ascending aortic dissection and other suspected traumatic injury to the aorta. TEE is also useful and has the advantage that it can be performed rapidly at the bedside in a critically ill patient who is not suitable for transport. TEE requires sedation and may not be feasible in patients with maxillofacial or cervical spine injuries. Although TTE cannot be used to exclude the diagnosis of aortic dissection, a limited and focused study can be performed more rapidly at the bedside than any other test, and visualization of a flap in the aortic root or ascending aorta can clinch the diagnosis. Magnetic resonance angiography is an alternative modality, but is not well suited for unstable patients due to the time required to perform the study. Aortography, once the gold standard, is now rarely performed out of concern for procedural complications in the setting of acute aortic injury. Definitive surgical repair is indicated for ascending aortic dissection or traumatic aortic rupture.

III. PENETRATING TRAUMA

- A. Gunshot wounds and stabbings are the most common types of penetrating trauma. The prognosis depends entirely on the extent of injury and the number of chambers involved. Overall mortality is estimated at 60% to 93% for gunshot wounds, 22% to 62% for knife injuries, and 25% for bolting instruments (i.e., nail guns). Less frequently, iatrogenic catheter-induced injury can occur in the setting of temporary or permanent pacemaker placement.
- B. As with blunt cardiac trauma, the clinical presentation tends to be one of **tamponade** or exsanguinating **hemorrhage**, depending on the integrity of the pericardium. **However, unlike in the case of blunt trauma, tamponade carries a favorable prognosis in penetrating trauma.** One series described a survival rate of 73% among patients with penetrating trauma with tamponade versus 11% among those without. Thrombus within the pericardium is thought to stabilize the rapid hemorrhagic shock associated with penetrating injuries. Pericardial lacerations may also seal spontaneously. Bleeding from the muscular, thicker walled left ventricle is also more likely to be self-limited, whereas injury to the relatively thin right ventricle or right atrium is more likely to be catastrophic and fatal. Knife wounds tend to be smaller and focal, whereas gunshot wounds tend to be larger, extensive, and more likely to present with frank hemorrhage.
- C. **The right ventricle is the chamber most often involved in penetrating trauma** because of its anterior location in the chest. As described for blunt trauma, penetrating trauma may result in laceration of the pericardium or myocardium, valves, coronary arteries, or the aorta.
- D. **Diagnosis.** In an unstable patient, a TTE should be obtained rapidly at the bedside. Although images may be suboptimal, both the sensitivity and the specificity of TTE for identifying cardiac abnormalities in this setting are 85% to 90%. A portable chest radiograph may reveal the presence of a pneumothorax or hemothorax.
- E. **Management.** After the diagnosis of penetrating cardiac trauma has been made, the patient should be transported as rapidly as possible to the operating room for definitive surgical repair. The infusion of saline and blood products should be continued as needed. Warming of fluids is often needed to prevent hypothermia associated with massive volume resuscitation. There is no role for serial pericardiocentesis in patients with trauma and pericardial effusion, but emergency pericardiocentesis is occasionally necessary if there are delays in reaching the operating room.

IV. SPECIAL CONSIDERATIONS

- A. **Indwelling foreign bodies and missile embolization.** Missile embolization from bullet fragments, air gun pellets, or shrapnel is an extremely rare complication from gunshot wounds or battlefield injuries. Data from the Vietnam conflict suggest that this phenomenon complicates 0.3% to 0.4% of all vascular missile injuries. Clinical suspicion for embolization should be raised in a scenario of multiple penetrating entrance wounds or a single penetrating entrance wound without a corresponding exit wound. The majority of patients with right heart or pulmonary embolization are asymptomatic, but up to 17.4% of patients develop chest pain, dyspnea, or hemoptysis. Up to 4% of patients may exhibit cardiac arrhythmias. Patients with undiagnosed indwelling foreign bodies may also develop subacute bacterial endocarditis as a latent presentation. Metallic missile fragments are usually radiopaque and detected on plain x-rays or a noncontrast CT scan. Intracardiac indwelling foreign bodies should be evaluated by TEE, especially when endocarditis is suspected. Ultimately, the decision to remove asymptomatic indwelling foreign bodies is made on a case-by-case clinical basis considering operative logistics and weighing risk against the potential benefit.
- B. **Device implants.** An awareness of device-related complications in the setting of cardiac trauma is important, given the expanding patient population with pacemakers and/or implantable defibrillators. Common complications in the setting of blunt trauma would include pocket hematoma, lead dislodgement, or fracture. Penetrating trauma could expose the generator and/or tunneled leads and lead to bleeding or secondary infection. Lead perforation is an uncommon but life-threatening complication manifested as tamponade. Hypotension and bradycardia should prompt concern for lead fracture or dislodgement, especially if the patient is known to be pace-maker dependent. Emergent transcutaneous or transvenous pacing is indicated if the underlying bradyarrhythmia is not hemodynamically tolerated. Device interrogation can also be performed at the bedside to assess pacer dependence and the functional status of all leads using computer equipment provided by the major manufacturers.

ACKNOWLEDGMENTS: *The author acknowledges Drs. Daniel Cantillon and John Hostetter for their contributions to earlier editions of this chapter.*

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Pregnancy and Cardiovascular Disease

- I. INTRODUCTION.** Maternal cardiac disease is a major risk factor for nonobstetric mortality and morbidity in pregnant women. Substantial progress in the management of congenital heart disease has occurred over recent decades, so the majority of females born with heart defects now survive into their reproductive years. Advances in obstetrics have also enabled pregnancy in older mothers in whom hypertension and acquired heart disease are more prevalent and can pose challenges for the pregnancy. Rheumatic heart disease is less common than in the past, but is still encountered, especially in immigrant populations in the United States, and may manifest clinically for the first time in pregnancy. Cardiac disease has significant bearing on both maternal and fetal outcomes, and it is therefore essential that cardiologists and internists have a working knowledge of the impact of pregnancy on various cardiac diseases on pregnancy and can tailor management appropriately. In most cases, the presence of maternal heart disease does not preclude successful pregnancy, although thorough discussion and planning regarding risks and management strategies should begin prior to conception wherever possible.
- II. NORMAL PHYSIOLOGIC CHANGES DURING PREGNANCY.** A series of cardiocirculatory changes occur in pregnancy and peripartum. These changes **usually begin during the early first trimester** (5 to 8 weeks), peak in the late second trimester, and tend to plateau thereafter until the postpartum period. This second trimester peak in hemodynamic adaptations tends to correlate with the onset of clinical manifestations of cardiac complications during pregnancy.
- A.** The **increase in blood volume** during pregnancy is attributed to estrogen-mediated stimulation of the renin–aldosterone system, leading to salt and water retention along with various other maternal and placental hormones. **The plasma volume expansion varies from 20% to 100% and averages around 50%.** The relatively greater increase in plasma volume as compared with red blood cell mass leads to the physiologic anemia of pregnancy, which usually manifests around 30 weeks.
- B.** **Cardiac output, stroke volume, and heart rate.** Table 38.1 summarizes the changes in heart rate, stroke volume, and cardiac output. **The cardiac output is estimated to increase by approximately 30% to 50% above baseline.** The increase is attributed to higher preload as a result of increased blood volume, decreased systemic vascular resistance, and an increase in maternal heart rate by 10 to 15 beats/min. During the third trimester, stroke volume and cardiac output are dependent on body position and increase in the lateral position (particularly left lateral) and decline in the supine position due to compression of the inferior vena cava by the gravid uterus.
- C.** **Blood pressure and systemic vascular resistance.** The decline in systemic vascular resistance causes blood pressure to begin to fall in the first trimester and reach a nadir of about 10 mm Hg below baseline by the end of the second trimester. The pulse pressure widens due to the greater fall in diastolic blood pressure than in systolic pressure. As many as 11% of women develop the **uterocaval syndrome** of pregnancy, with a significant and symptomatic drop in blood pressure when lying supine

TABLE 38.1 Normal Hemodynamic Changes during Pregnancy and Postpartum Period

Changes during different phases of pregnancy					
Hemodynamic parameter	First trimester	Second trimester	Third trimester	Labor and delivery	Postpartum
Heart rate	↑5–10%	↑10–15%	↑15–20%	↑20–30%	↓
Stroke volume	↑5–30%	↑30–40%	↓20–30%	↑300–500 mL with each contraction	↓
Cardiac output	↑5–30%	↑30–40%	↑> 40%	↑50%	Initial ↑ then ↓
Systolic BP	↔to ↓	↓	↔to ↑	↑	Baseline
Diastolic BP	↔to ↓	↓	↓to ↔	↑	Baseline
Systemic vascular resistance	↓10–30%	↓30–40%	↓30–40%	↑	Baseline

BP, blood pressure.

due to vena caval compression. **Weakening of the vascular walls** of the medium and large muscular arteries occurs because of decreased collagen deposition due to estrogen release and the effects of circulating elastase and relaxin. This makes pregnant women more susceptible to aortic dissection, especially in individuals with abnormally weak aortic tissue such as in Marfan syndrome. The addition of low-resistance vessels in the uteroplacental bed also contributes to the decrease in afterload.

D. A hypercoagulable state with decreased protein S, increased stasis, and venous hypertension is also observed.

E. Hemodynamic changes during labor and delivery. Each uterine contraction displaces about 300 to 500 mL of blood into the maternal general circulation (autotransfusion). There is an increase in stroke volume and heart rate, with cardiac output increasing by approximately 75% above baseline during contractions. Blood pressure and oxygen consumption also rise. The magnitude of these changes will be influenced by the mode of delivery—vaginal versus cesarean section—and also by the method of anesthesia and analgesia.

F. Hemodynamic changes postpartum. Despite the blood loss during delivery (averaging 300 to 400 mL for vaginal delivery and 500 to 800 mL for cesarean section), there is a **temporary increase in effective venous return due to the relief of caval compression and autotransfusion**. This may lead to an increase in stroke volume and cardiac output, resulting in augmentation in renal blood flow and a brisk diuresis. In women with preexisting cardiac disease, these rapid hemodynamic shifts may cause profound clinical deterioration. The hemodynamic changes associated with pregnancy usually persist for a few weeks postpartum and it may take up to 12 to 24 weeks for the parameters to return to their prepregnancy baseline.

III. CARDIOVASCULAR EVALUATION IN PREGNANCY

A. History. Fatigue, dyspnea, ankle swelling, and reduced exertional capacity are common in normal pregnancy and can mimic cardiac disease. Chest pain, orthopnea, or paroxysmal nocturnal dyspnea may represent cardiac pathology.

B. Physical examination. Table 38.2 highlights the important cardiac findings in normal pregnancy. Signs of jugular venous distention, displaced point of maximal

impulse, and peripheral edema are common in normal pregnancy. Normal auscultatory findings in pregnancy include exaggerated physiologic splitting of S_2 , a physiologic S_3 , a physiologic systolic murmur in the pulmonic area, and the continuous murmurs of “mammary soufflé” or a cervical venous hum. Examination findings that are not physiologic include an S_4 , a loud systolic murmur, a purely diastolic murmur, and fixed splitting of S_2 or pulmonary crackles.

- C. **Noninvasive testing** with echocardiography is considered safe in pregnancy and findings are as given in Table 38.2. Chest radiography should be performed only when absolutely necessary and with shielding of the pelvic area with protective lead. Magnetic resonance imaging is sometimes used for the diagnosis of cardiac disorders; its safety profile in pregnancy is unknown, and it should be avoided if possible.

TABLE 38.2 Findings in Normal Pregnancy

Symptoms

Fatigue

Dyspnea

Palpitations

Reduced exercise tolerance

Orthopnea

Lower extremity edema

Physical examination

Hyperventilation

Lower extremity edema

Distended neck veins with prominent *a* and *v* waves and brisk *x* and *y* descents

Increased heart rate and wide pulse pressure

Upward and leftward deviation of point of maximal impulse

“Flow” murmurs (pulmonic and aortic)

Mammary soufflé (left sternal border, continuous murmur)

Increased first heart sound and exaggerated splitting of second heart sound

Third heart sound

Electrocardiographic findings

Sinus tachycardia

Leftward axis deviation

Increased R/S ratio in leads V_1 and V_2

Repolarization changes

Echocardiographic findings

Increased left ventricular diastolic dimension

Increased left ventricular wall thickness

Mild increase in contractility

Moderate increase in size of right atrium, right ventricle, and left atrium

Functional pulmonary, tricuspid, and mitral regurgitation

Small pericardial effusion

D. Invasive testing with pulmonary artery catheterization (without fluoroscopy) can be utilized during pregnancy, labor, delivery, and the postpartum period for invasive monitoring and can be very useful for patients who suffer hemodynamic deterioration. Cardiac catheterization during pregnancy is rarely needed, except in the setting of acute myocardial infarction (MI) or to permit balloon valvuloplasty. Fluoroscopy and cine time should be minimized and direct irradiation to the fetus avoided. Vascular access from the arm rather than the leg is preferred whenever feasible.

IV. RISK ASSESSMENT AND GENERAL PRINCIPLES OF MANAGEMENT. One of the most important steps in managing a patient with heart disease who is considering pregnancy is to establish the level of maternal and fetal risk. This involves a multidisciplinary approach, with preconception counseling, contraception advice, and discussion of potential maternal and fetal acute and long-term morbidity and mortality. Baseline functional class, severity of cardiac disease, left ventricular function, and pulmonary pressures should guide the risk assessment. Table 38.3 delineates a stepwise approach for management of women with preexisting cardiac disease, and Table 38.4 lists high-risk predictors. **Maternal New York Heart Association (NYHA) class II symptoms or higher, left ventricular ejection fraction < 40% or left-sided obstruction** are factors known to be predictive of neonatal complications, including premature birth,

TABLE 38.3 Basic Management Principles for Pregnant Women with Valvular Heart Disease

Risk assessment

Preconception

- Thorough history of cardiac symptoms and arrhythmias
- Baseline exercise tolerance and functional class
- Baseline electrocardiogram and echocardiography with ventricular function and pulmonary pressures
- Detailed discussion with the patient about the potential risks to self and fetus

During pregnancy

- Follow-up evaluation at least once per trimester
- Close monitoring of new symptoms or change in functional class
- Serial echocardiography for development of any new symptoms or signs

Treatment

Preconception

- Effective and safe contraception until pregnancy is desired
- Consider valve repair or replacement, correction of anomaly prior to conception if pregnancy poses significant risk of worsening clinical status
- Adjust medications to prevent adverse fetal side effects

During pregnancy

- Minimize medication use to only those absolutely required and discontinue or replace medications contraindicated in pregnancy
- If symptoms worsen and if indicated, consider correction of anomaly or valve repair or replacement

(Continued)

TABLE 38.3 Basic Management Principles for Pregnant Women with Valvular Heart Disease (Continued)**Labor and delivery**

- Invasive monitoring as needed
- Cesarean section for obstetric indication
- Monitor for decompensated heart failure and pulmonary edema and treat accordingly

Postpartum

- Adjust and optimize medications
- Consider correction of anomaly or valve repair or replacement if indicated
- Treat postpartum anemia
- Counseling and contraception for future pregnancies

Adapted from Stout KK, Otto CM. Pregnancy in women with valvular heart disease. *Heart*. 2007;93:552–558.

TABLE 38.4 Risk Predictors of Adverse Maternal and Fetal Outcomes

- Prior cardiac events or medication
- Prior arrhythmia
- NYHA class II or higher, or cyanosis
- Ejection fraction < 40%
- Pulmonary hypertension (pulmonary artery systolic pressure > 50% systemic pressure)
- Severe aortic stenosis (valve area < 1.5 cm², Doppler jet velocity > 4 m/s)
- Symptomatic or severe mitral stenosis
- Severe aortic or mitral regurgitation with NYHA class III or IV symptoms
- Hypertrophic obstructive cardiomyopathy
- Maternal anticoagulation

intrauterine growth restriction, respiratory distress syndrome, and death. Formal risk prediction scores include Cardiac Disease in Pregnancy (CARPREG), which is composed of four clinical features (prior arrhythmia or cardiac event, NYHA functional class > II or cyanosis, left heart obstruction, systemic left ventricular dysfunction with LVEF < 40%) with maternal cardiac event rates of 5%, 27%, and 75% for 0, 1, and > 1 of the features, respectively, and the more recent ZAHARA predictors derived from a large population of congenital heart disease patients.

Management of the pregnant patient with heart disease is a team effort involving the patient's primary care physician, high-risk obstetric team, and cardiologist, with active participation of the patients. **Prophylactic intervention for cardiac lesions that significantly increase the risk of pregnancy should be performed where appropriate and feasible before pregnancy is contemplated.** Most patients with relatively low-risk cardiac conditions are successfully managed throughout pregnancy, labor, and delivery with conservative medical measures designed to optimize intravascular volume and systemic

loading conditions. Simple measures help, such as bed rest and avoidance of the supine position. Medications should be used judiciously and only when absolutely required during pregnancy. Drugs that are contraindicated in pregnancy should be discontinued before conception if pregnancy is contemplated. **In certain conditions such as cyanotic congenital heart disease, Eisenmenger syndrome, or severe pulmonary hypertension, pregnancy should be strongly discouraged, as patients with these conditions do not tolerate the hemodynamic changes of pregnancy.**

Specific lesions and their management in pregnancy are described later. The list, although extensive, is not complete, as a detailed description of every lesion is beyond the scope of this chapter.

- V. PREGNANCY IN WOMEN WITH CONGENITAL HEART DISEASE.** In general, patients with noncyanotic congenital heart disease have a better outcome with pregnancy compared with patients with cyanotic disease. Where applicable, patients should be made aware of the potential inheritability of the congenital disease. The 2007 American Heart Association (AHA) endocarditis guidelines do not recommend the use of prophylactic antibiotics for vaginal delivery, even in high-risk patients, such as those with complex congenital heart disease or surgically constructed systemic–pulmonary shunts. However, owing to the difficulty in predicting complicated deliveries and the potential complications of endocarditis, some authors still suggest antibiotic prophylaxis as reasonable for all patients with congenital heart disease, except in isolated secundum atrial septal defects (ASDs) and corrected patent ductus arteriosus (PDA). The 2008 American College of Cardiology/AHA (ACC/AHA) guidelines on the management of adults with congenital heart disease do suggest antibiotics at the time of membrane rupture prior to vaginal delivery for patients with prosthetic cardiac material or unrepaired/palliated cyanotic defects.
- A. ASD and patent foramen ovale (PFO).** Isolated ASD or PFO is usually well tolerated in pregnancy and considered low risk in general. Paradoxical pulmonary embolism during pregnancy has been reported. Ideally, an ASD with a significant shunt ($> 1.5:1$) should be corrected prior to pregnancy. Secundum ASD that is repaired prior to pregnancy is not associated with an increased risk of complications.
- B. Ventricular septal defect (VSD).** Isolated VSD without pulmonary hypertension is usually well tolerated during pregnancy, and correction of VSD prior to pregnancy and before development of pulmonary hypertension eliminates the risk. In pregnant patients with VSD and pulmonary hypertension, a drop in blood pressure during or after delivery can result in transient shunt reversal. This may be prevented by close monitoring of blood pressure, volume replacement, and the use of vasopressors, if necessary. VSD is commonly inheritable.
- C. Patent ductus arteriosus.** PDA without pulmonary hypertension usually has a favorable outcome. In patients with pulmonary hypertension, the management principles are similar to those with VSD.
- D. Coarctation of aorta (COA).** Coarctation, although usually associated with favorable outcomes, has been associated with severe hypertension, congestive heart failure, or aortic dissection during pregnancy. There is an association with congenitally bicuspid aortic valves (AVs). It is also associated with circle of Willis aneurysms, and cerebral hemorrhage from rupture of an aneurysm during pregnancy is possible. Limiting physical activity and controlling blood pressure may prevent complications such as cerebral hemorrhage and dissection. β -Blockers are usually the antihypertensive drugs of choice, although care should be taken not to lower the blood pressure excessively as this may compromise uteroplacental circulation. Significant COA with evidence of systemic hypertension, heart failure, or a peak gradient > 20 mm Hg should be corrected prior to pregnancy. Women who underwent prior surgical repair of a coarctation remain at risk for dissection, as the aortic wall is still abnormally weak. Correction of COA during pregnancy is indicated in patients with severe uncontrollable hypertension or heart failure and may be performed percutaneously.

- E. **Congenital aortic stenosis (AS).** A congenitally bicuspid AV is one of the most common causes of AS. These patients should be screened for other cardiac malformations including COA. The details of management are described later in Section VI.
- F. **Pulmonic stenosis.** Isolated pulmonic stenosis is usually well tolerated in pregnancy. It should be corrected prior to pregnancy if severe (peak gradient > 60 mm Hg). Percutaneous balloon valvotomy during pregnancy may be required in patients with severe right ventricular failure.
- G. **Ebstein anomaly.** Noncyanotic Ebstein anomaly is usually well tolerated. Cyanotic patients are at very high risk for maternal heart failure and fetal prematurity or death. During labor and delivery, care should be taken to prevent a drop in blood pressure, and close hemodynamic monitoring is required along with rest, oxygen, and blood gas monitoring. It is sometimes associated with Wolff-Parkinson-White syndrome and pregnancy may precipitate supraventricular arrhythmias.
- H. **Tetralogy of Fallot (TOF).** Women with TOF who have undergone successful repair during childhood with little or no residual outflow tract gradient, no pulmonary hypertension, and preserved ventricular function usually tolerate pregnancy well. In women with uncorrected or only partially corrected TOF, increased blood volume during pregnancy with increased venous return and decreased systemic vascular resistance may result in right to left shunt and cyanosis. A similar process may also occur with a fall in blood pressure during labor and delivery. **The outcome of pregnancy is very poor for both mother and fetus once cyanosis occurs.** It is also associated with high rates of premature labor, spontaneous abortion, and fetal growth restriction. The risk of a cardiac defect in the neonate ranges from 3% to 17%; genetic counseling and screening for the 22q11 deletion should be offered to women with TOF. Patients with residual lesions after partial correction such as pulmonic regurgitation, right ventricular outflow obstruction, and right ventricular dysfunction are at risk for heart failure and arrhythmia during pregnancy. Poor prognostic signs include maternal hematocrit above 60%, arterial oxygen saturation below 80%, right ventricular hypertension, and syncopal episodes. Patients with cyanotic disease should be strongly encouraged against pregnancy.
- I. **Eisenmenger syndrome.** **Pregnancy in women with Eisenmenger syndrome is associated with a very high maternal mortality in the range of 30% to 50%, with a 50% risk of fetal loss if the mother survives.** Maternal death occurs mostly between the first few days to first few weeks following delivery due to rapid hemodynamic deterioration. Therefore, patients with Eisenmenger syndrome should be strongly discouraged against pregnancy. Early therapeutic abortion may be considered given the danger to the mother. If pregnancy is continued, close monitoring is necessary. Restricted physical activity, continuous oxygen use for at least the third trimester, and consideration of pulmonary vasodilating drugs are recommended. Due to increased incidence of thromboembolism, anticoagulant therapy is recommended, starting from the third trimester until 4 weeks postpartum. An attempt to shorten the second stage of labor by the use of forceps or vacuum should be made; cesarean delivery is associated with significantly higher mortality.

VI. VALVULAR HEART DISEASE AND PREGNANCY. Lesions generally associated with high maternal and/or fetal risks include symptomatic mitral stenosis (MS), severe AS (with or without symptoms), NYHA class III and IV symptoms with mitral or aortic regurgitation, valvular disease with severe pulmonary hypertension or left ventricular dysfunction, mechanical prosthetic valve requiring anticoagulation, Marfan syndrome, and hypertrophic cardiomyopathy (HCM). Lesions generally associated with low maternal or fetal risk include asymptomatic AS with normal ventricular function, mitral valve prolapse, mild MS, and NYHA functional class I or II mitral or aortic regurgitation.

- A. Mitral stenosis.** MS is one of the most common rheumatic valvular lesions seen in pregnancy and is poorly tolerated. The physiologic changes in pregnancy with increased blood volume and heart rate can lead to an increased pressure gradient across the valve and decreased filling time, respectively. This leads to increases in left atrial pressure and ensuing symptoms of pulmonary edema with dyspnea, orthopnea, and paroxysmal nocturnal dyspnea. Occurrence of atrial fibrillation with a rapid ventricular rate often causes further clinical deterioration. Patients with moderate to severe MS are more susceptible to these hemodynamic disturbances. The rapid increase in venous return during labor and delivery may cause significant decompensation and requires very close monitoring.

Management depends upon the severity of stenosis, symptoms, and time of diagnosis. **If MS is diagnosed prior to pregnancy, patients with severe MS (valve area < 1 cm²) or moderate symptomatic stenosis should be offered percutaneous mitral balloon valvuloplasty (PMBV) or valve repair if PMBV is not feasible, before pregnancy.** In patients with moderate asymptomatic stenosis, careful assessment of symptoms and exercise tolerance testing can help guide the decision for pre-pregnancy intervention. In patients with mild MS (valve area > 1.5 cm²), pregnancy is usually tolerated with a favorable outcome. **Optimal management of an already pregnant patient with MS is aimed at reducing heart rate and left atrial pressure.** β -Blockers are the drug of choice, and selective β_1 -adrenergic drugs are preferred over nonselective β -blockers to avoid β_2 -adrenergic-mediated uterine relaxation. In patients with atrial fibrillation (Table 38.5), digoxin may also be used for ventricular rate control. Electrical cardioversion can be performed safely during pregnancy if the hemodynamic status warrants restoration of sinus rhythm. Left atrial pressure may be controlled by salt restriction and very judicious use of diuretics (excessive use can lead to reduced uteroplacental perfusion). In patients with symptoms and signs of clinical deterioration despite optimal medical therapy, PMBV may be necessary during pregnancy. This should be avoided in the first trimester if possible and proper abdominal and pelvic shielding must be used. Echocardiographic guidance by an experienced operator can limit radiation exposure. In cases with severe MS refractory to medical therapy and not amenable to PMBV, mitral valve repair or replacement may be considered. Cardiopulmonary bypass during pregnancy carries a risk of fetal demise and should be performed with normothermic perfusion and high flow volumes with the mother in the lateral decubitus position to maximize placental perfusion.

Most patients with MS can safely undergo vaginal delivery. Patients with symptomatic moderate and severe MS should have hemodynamic monitoring and optimization guided by pulmonary artery catheterization during labor and delivery

TABLE 38.5 ACC/AHA Guidelines for Management of Atrial Fibrillation in Pregnancy

Class I (benefits >>> risk) procedure/treatment should be performed/administered

Digoxin, a β -blocker, or a nondihydropyridine calcium channel antagonist is recommended to control the rate of ventricular response in pregnant patients with AF

Direct current cardioversion is recommended in pregnant patients who become hemodynamically unstable due to AF

Protection against thromboembolism is recommended throughout pregnancy for all patients with AF (except for those with lone AF and/or low thromboembolic risk). Therapy (anticoagulant or aspirin) should be chosen according to the stage of pregnancy

and in the immediate postpartum period (12 to 24 hours) when relief of uterocaval obstruction can cause increased venous return and pulmonary edema. Epidural anesthesia is usually better tolerated than general anesthesia, and cesarean section is generally performed for obstetric indications only. Young pregnant women with a previous history of rheumatic carditis should continue to undergo penicillin prophylaxis postpartum as they did in the nonpregnant state.

- B. Mitral regurgitation (MR).** The most common cause of MR during pregnancy is either rheumatic heart disease or mitral valve prolapse. MR is usually well tolerated in pregnancy because the fall in systemic vascular resistance leads to a decreased left ventricular afterload. Atrial fibrillation and hypertension may sometimes cause acute symptomatic decompensation.

Asymptomatic patients are managed conservatively without any therapy, and patients with left ventricular dysfunction and decompensated heart failure are managed with diuretics and digoxin. In the peripartum period, increased venous return and systemic vascular resistance sometimes lead to decompensation requiring diuretics and afterload reduction. Angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) are contraindicated during pregnancy because of their teratogenic effect. Hydralazine may be used in patients with MR and hypertension for afterload reduction. Acute MR due to ruptured chordae is rare in pregnancy and is usually not well tolerated. It may require intraaortic balloon pump placement and emergent surgery.

- C. Aortic stenosis.** The most common etiology for AS in childbearing age is a congenitally bicuspid valve. Rheumatic AS is less common, but may occur in conjunction with MS. Mild-to-moderate AS with preserved left ventricular function is usually well tolerated during pregnancy. **Severe AS (i.e., AV area < 1.0 cm² and mean gradient > 50 mm Hg) significantly increases the risk during pregnancy and may lead to significant hemodynamic deterioration, heart failure, and premature delivery.** Patients with severe AS should therefore be counseled against pregnancy or undergo surgery prior to conception. Symptoms such as chest pain, syncope, or dyspnea usually present late in the second trimester or early in the third trimester. Patients with bicuspid AV and aortic root dilation, especially those with coarctation of the aorta, are at increased risk for spontaneous aortic dissection.

When severe symptomatic AS is diagnosed during pregnancy, PABV should be performed before labor and delivery. Although PABV may reduce the risk of decompensation in patients with severe AS, it has limited durability and only suffices as a temporizing measure until the patient can safely undergo AV replacement. Aortic insufficiency that occurs as a postprocedural complication of PABV is usually well tolerated during labor and delivery.

Close invasive hemodynamic monitoring, as in patients with MS, may be required. Spinal anesthesia and epidural anesthesia are discouraged during labor and delivery because of their vasodilatory effects.

- D. Aortic regurgitation/aortic insufficiency (AI).** AI is generally well tolerated in pregnancy due to the combination of reduced systemic vascular resistance and shortened diastole with the rise in heart rate. In a young woman, AI may be due to a congenitally bicuspid valve, an infective endocarditis, an autoimmune disorder (e.g., rheumatoid arthritis), or a dilated aortic annulus. Marfan syndrome should always be excluded due to its implications regarding aortic root stability. AI without left ventricular dysfunction is usually well tolerated in pregnancy owing to decreased systemic vascular resistance and increased heart rate causing a shorter diastole and therefore reducing regurgitation. In symptomatic patients with decompensated heart failure, diuretics, digoxin, and hydralazine may be used for afterload reduction.
- E. Hypertrophic cardiomyopathy.** Most asymptomatic patients with HCM have a favorable outcome during pregnancy. The overall morbidity and mortality with HCM and pregnancy is, however, still higher than that in the general population. Symptoms such as chest pain, palpitations, worsening dyspnea, and syncope may

occur and are more common in women who were symptomatic prior to pregnancy. Various arrhythmias, including supraventricular tachycardias, atrial fibrillation with hemodynamic deterioration and fetal distress, and ventricular fibrillation, have also been reported. There is an increased risk of fetal prematurity. Women should receive genetic counseling before conception whenever possible; the risk of inheriting the disease may approach 50% in certain familial forms of HCM.

Management depends on the presence of symptoms and the severity of left ventricular outflow obstruction. Blood loss, volume depletion, and vasodilators should be avoided, and medications should be reserved for symptoms of heart failure and arrhythmias. β -Blockers are usually the drug of choice for symptomatic patients. Patients with a history of syncope, life-threatening arrhythmias, or a family history of sudden cardiac death should be considered for prophylactic implantable defibrillators prior to pregnancy due to the potential arrhythmogenic effect of pregnancy.

Vaginal delivery is considered safe, but tocolytics with β -adrenergic properties and prostaglandins should be avoided. Epidural anesthesia is used with caution because of the peripheral vasodilatory effect, and excessive blood loss should be promptly repleted with fluids or blood transfusion. The brisk diuresis immediately postpartum may lead to a rapid decrease in intravascular volume and, therefore, a symptomatic increase in outflow tract gradient. This can be avoided by gentle intravenous (IV) hydration decreasing over 24 to 48 hours postpartum to achieve a euvolemic state.

- F. Prosthetic heart valves.** The selection of an appropriate prosthetic valve in a woman of childbearing age is controversial. **Where possible, the patient's own valve should be conserved or repaired. When valve replacement is necessary, bioprosthetic and homograft valves are safer for mother and child, although their use is associated with an increased risk of degeneration in younger people, which may also be accelerated by pregnancy.** Mechanical valves, and their anticoagulation requirement, confer increased maternal mortality, morbidity, and fetal loss. A detailed preconception discussion with the patient should include potential complications during pregnancy, the potential for harm to the fetus and/or mother with various anticoagulation strategies, and recognition of the signs and symptoms of valve dysfunction or heart failure. The risk of complication during pregnancy depends on the type of valve, position of the valve, and pre-pregnancy cardiac function and functional capacity. Patients with NYHA class III or IV symptoms should be strongly advised against pregnancy. In pregnant patients with well-functioning bioprosthetic valves, the management is similar to that in patients with native valves. Patients should be made aware of the possibility of valve degeneration and should be monitored for signs and symptoms of this.

Pregnancy should be discouraged in patients with mechanical heart valves. In pregnant patients with mechanical heart valves, management of anticoagulation is challenging. Pregnancy is a thrombogenic state, and thrombosis has been reported in up to 10% to 15% of patients with mechanical prosthetic valves during pregnancy. The incidence is particularly high in patients with older generation valves (Björk-Shirley and Starr-Edwards) in the mitral position, but complications and deaths have also been reported in newer generation valves in the aortic position. Patients with prosthetic valves and poor left ventricular function are also at risk for heart failure from volume overload during pregnancy and arrhythmias.

The management of anticoagulation during pregnancy is discussed in detail in a separate section of this chapter.

VII. OTHER CARDIOVASCULAR DISEASES AND PREGNANCY

- A. Hypertensive disorders in pregnancy.** Hypertensive disorders complicate 8% to 10% of pregnancies and are a major cause of maternal and perinatal morbidity and mortality. Hypertensive disorders can be broadly classified into chronic hypertension, gestational hypertension, and the preeclampsia-eclampsia spectrum.

Chronic hypertension is defined as blood pressure of 140/90 mm Hg or greater before pregnancy, before 20 weeks of gestation, or persisting beyond postpartum day 42. It is associated with increased maternal and fetal morbidity and elevates the risk of preeclampsia development. Blood pressure treatment is aimed at minimizing maternal end-organ damage (such as left ventricular hypertrophy, renal failure, or intracerebral hemorrhage), balanced against concerns that excessive pressure lowering may negatively impact fetal growth. The threshold for initiating drug therapy is controversial and differing recommendations are offered by the various international society guidelines.

Gestational hypertension is defined as hypertension induced by pregnancy and diagnosed after 20 weeks of gestation and usually resolving within 42 days postpartum. The major clinical task is vigilance in the detection of any features of preeclampsia, including development of significant new-onset proteinuria, an increase in preexisting proteinuria, or any suggestive symptoms. Gestational hypertension may portend the development of future primary hypertension and cardiovascular disease, but is otherwise usually associated with good maternal and fetal outcomes.

Preeclampsia occurs in 2% to 5% of all pregnancies, 10% of first pregnancies, and 20% to 25% of women with chronic hypertension. It can be diagnosed with a blood pressure above 140/90 mm Hg, proteinuria exceeding 300 mg per 24 hour urine collection (or > 30 mg/mmol in a spot urine sample), an increase in proteinuria or loss of blood pressure control in a woman with chronic hypertension, or the onset of headache, blurred vision, abdominal pain, transaminitis, or hypertension. However, rare cases occur without significant proteinuria or an elevated blood pressure. Onset is usually in the third trimester with resolution after delivery, although postpartum cases are reported. Risk factors include maternal age over 40 years, Black ethnicity, nulliparity, multiparity, first pregnancy with the male partner, prior hypertension or preeclampsia, obesity, diabetes, chronic kidney disease, thrombophilia, systemic lupus erythematosus, or a history of migraines. Patients with preeclampsia usually require hospitalization for IV magnesium sulfate to prevent seizures, bed rest, close fetal monitoring, and sometimes corticosteroids for acceleration of fetal lung maturity. The pathology involves aberrant invasion of myometrial arteries, resulting in unusually resistive spiral arteries and placental hypoperfusion. Although the etiology remains incompletely understood, angiogenic and antiangiogenic placental peptides (including PAPP-A, PIGF, sFlt-1, sEng, and PP-13) are providing insights into the pathophysiology of preeclampsia and may establish a diagnostic role as biomarkers.

Eclampsia is the development of grand mal seizures in a woman with preeclampsia. When preeclampsia is accompanied by poor prognostic features such as severe hypertension, **HELLP syndrome** (hemolysis, elevated liver enzymes, low platelets), placental abruption, cerebral hemorrhage, pulmonary edema, or renal failure, the fetus must be delivered immediately. Expert opinion supports delivery within 24 hours for women with treatment-resistant hypertension or maternal or fetal compromise, regardless of gestational age or fetal lung maturity. Beyond 34 weeks of gestation or in cases where fetal lung maturity has been achieved, delivery should occur without delay. Because of the high risk of maternal and fetal mortality and morbidity, these patients should be managed at a tertiary care center with high-risk obstetrics and neonatology.

Table 38.6 lists different drug therapies used to treat hypertension in pregnancy. IV labetalol is the drug of choice for acute hypertensive urgency or emergency in pregnancy. Hydralazine may also be used as a vasodilator. Sodium nitroprusside is usually avoided, especially in later stages of pregnancy, due to concern for fetal cyanide toxicity if used for more than 4 hours and should be used only as a last resort in cases where emergent control of blood pressure is required. **Methyldopa, labetalol, and nifedipine are the most commonly used oral antihypertensive agents during pregnancy, although there is a paucity of evidence for optimal blood pressure targets or drug choices.** It is generally agreed that **systolic blood pressures of 150 to 160 mm Hg and/or diastolic blood pressures of 100 to 100 mm Hg and above should be treated.**

TABLE 38.6 Drug Therapy for Hypertension in Pregnancy

Drugs for hypertensive urgency and emergencies			
Drug	Mechanism of action	Dosing	Comments
Labetalol	α - β -Adrenergic blocker	20–80 mg IV q10-20min (up to 300 mg)	Appears efficacious; widely used; scant safety data
Hydralazine	Vasodilator	5–10 mg IV q15-30min	Efficacious and safe during pregnancy and lactation
Sodium nitroprusside	Arterial-veno dilator	0.5–5.0 μ g/kg/min	Concern for fetal thiocyanate toxicity
Drugs for long-term treatment of hypertension			
Drug	Mechanism of action	Dosing	Comments
Methyldopa	Central α_2 -agonists	250 mg tid up to 4 g/d	Most commonly used; safety well established; drug of choice
Labetalol	α - β -Adrenergic blocker	100 mg tid up to 2,400 mg/d	Appears efficacious; widely used; scant safety data
Nifedipine	Calcium channel blocker	once daily sustained release dosing up to 120mg/d	Short-acting nifedipine may precipitate severe hypotension and should be avoided; hypotension also possible with sustained release

Adapted from Elkayam U. Pregnancy and cardiovascular disease. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 7th ed. Philadelphia, PA: Elsevier Saunders; 2005:1965–1982.

- B. Marfan syndrome.** Marfan syndrome is a connective tissue disorder resulting from mutations in the fibrillin gene. It is inherited in an autosomal-dominant fashion. The clinical manifestations include skeletal abnormalities, ectopia lentis, and cardiovascular abnormalities, such as aortic root dilation with or without aortic regurgitation, aortic dissection, and mitral valve prolapse. **Aortic dissection** and rupture are the most feared complications of pregnancy in patients with Marfan syndrome due to hormonal influence on aortic wall integrity. Dissection is more likely to occur during the **third trimester and during labor and delivery and peaks at 3 to 20 days postpartum**.

Screening echocardiography should be performed before pregnancy. **Enlargement of the aortic root to more than 4.0 to 4.5 cm elevates the risk of aortic dissection and rupture from moderate risk to high risk.** Elective repair of the aortic root before conception is strongly advised with a root dimension above 4.5 cm; management should be individualized in the range 4.0 to 4.5 cm. The aortic root should be monitored by serial echocardiography during pregnancy.

Medical management during pregnancy involves the use of **β -blockers** throughout pregnancy to reduce the risk of aortic rupture, careful control of blood pressure, adequate analgesia during labor and delivery, and consideration of general anesthesia and cesarean section at the time of delivery to maximize hemodynamic control. Women with Marfan syndrome without cardiac abnormalities have a low complication rate and can usually tolerate normal vaginal delivery with spinal or epidural anesthesia to minimize pain and hypertension.

- C. Aortic dissection.** Aortic dissection during pregnancy has been reported in women with Marfan syndrome, systemic hypertension, coarctation of the aorta,

Turner syndrome, and cocaine use. It occurs most commonly in the third trimester and the peripartum period. Transesophageal echocardiography is the key diagnostic tool, and a β -blocker is the preferred medication for management during pregnancy.

- D. Coronary artery disease.** **MI during pregnancy is rare**, occurring in 6.2 per 100,000 deliveries in the United States in 2000 to 2002. The possibility of MI should always be entertained in a pregnant or immediately postpartum woman, especially if her symptoms and electrocardiogram are suspicious for coronary ischemia. **Most MIs occur during the third trimester in older women who have had multiple prior pregnancies.** *Coronary spasm, in situ coronary thrombosis, and coronary dissection are more frequently the underlying precipitants of MI* than classic obstructive atherosclerosis. Acute MI may be the initial clinical manifestation of an underlying hypercoagulable state, such as the antiphospholipid antibody syndrome. The diagnosis and management of acute MI in the pregnant patient should follow the guidelines established for the general population.

Medical therapy for acute MI must be modified in the pregnant patient. Thrombolytic agents increase the risk of maternal hemorrhage substantially (8%). Low-dose aspirin, β -blockers, and nitrates are considered relatively safe. Short-term heparin administration has not been associated with increased maternal or fetal adverse effects. ACE-Is, ARBs, and statins are contraindicated during pregnancy; there is no established safety data for clopidogrel or glycoprotein IIb/IIIa inhibitors. Coronary angiography should be performed only when emergent angioplasty or coronary artery bypass grafting is anticipated during pregnancy and, if possible, avoided in the first trimester. In general, bare metal (rather than drug-eluting) stents should be used if percutaneous intervention is necessary during pregnancy, as clopidogrel will need to be discontinued peripartum.

- E. Arrhythmias.** The most frequent rhythm disturbances, premature atrial complexes and premature ventricular complexes, are not associated with adverse maternal or fetal outcomes and do not require antiarrhythmic drug therapy. Atrial fibrillation and atrial flutter are rare during pregnancy. Rate control may be achieved with digoxin and β -blockers. Direct current cardioversion may be performed safely during any stage of pregnancy. Anticoagulation is recommended for chronic atrial fibrillation in the setting of underlying structural heart disease. **Atrioventricular nodal reentrant tachycardia** is the most common supraventricular arrhythmia in pregnant and nonpregnant women. It can lead to hemodynamic deterioration in women with underlying heart disease owing to rapid rates. Adenosine may be administered safely to the pregnant patient for both diagnostic and therapeutic purposes.

Ventricular tachycardia (VT) is rare during pregnancy. It may, however, be the presenting manifestation of peripartum cardiomyopathy (PPCM). VT has also been associated with thyrotoxicosis and hyperemesis gravidarum. Most antiarrhythmic medications used to treat VT are safe during pregnancy, **except for amiodarone**, which should be used with extreme caution and only for arrhythmias not responding to other medications, as it may lead to **neonatal hypothyroidism**. Bradyarrhythmias are uncommon during pregnancy. Complete heart block may be acquired or congenital. Pacemaker support is not usually required, unless the bradyarrhythmia is symptomatic or causes hemodynamic deterioration.

- F. Peripartum cardiomyopathy.** This is defined as the development of idiopathic left ventricular systolic dysfunction in the last month of pregnancy or within 5 months of delivery, in the absence of any identifiable or preexisting cause of heart failure. The incidence of PPCM in the United States is estimated to be 1 in 3,000 to 4,000 live births and is **more common in women older than 30 years**. The following risk factors for PPCM have been proposed: **multiparity, history of preeclampsia, eclampsia, or postpartum hypertension, African descent, low socioeconomic status, or tocolytic therapy with β -agonists**. Symptoms include fatigue, dyspnea on exertion, orthopnea, nonspecific chest pain, peripheral edema, and abdominal discomfort

and distention. PPCM has long been regarded as an idiopathic disease, but recent research has implicated a 16 kDa protein produced from cleavage of prolactin under oxidative stress, which is observed in higher levels in patients with PPCM. Bromocriptine, which inhibits prolactin secretion, has been administered with favorable outcomes in a small series of patients with PPCM. Standard management of pregnant patients presenting with decompensated heart failure includes oxygen, diuretics, digoxin, and vasodilators. ACE-Is and ARBs are absolutely contraindicated in pregnancy but should be commenced postpartum.

The prognosis after development of PPCM is variable. **Approximately 50% of women completely recover normal heart size and function, usually within 6 months of delivery.** The remainder either experience stable left ventricular dysfunction or continue to experience clinical deterioration. Estimated maternal mortality ranges from 10% to 50%. Women with PPCM and **persistent left ventricular dysfunction, or whose left ventricular ejection fraction was below 25% at initial presentation,** are at **very high risk for complications in a subsequent gestation** and should be counseled to avoid further pregnancies. Patients with severe cardiac dysfunction and decompensation should be evaluated for cardiac transplantation or mechanical support after pregnancy.

- G. Primary pulmonary hypertension.** This is associated with **very high maternal mortality (30% to 40%) and poor fetal outcomes.** Worsening of symptoms occurs in the second and third trimesters, and death is usually from right ventricular failure or arrhythmias. Pregnancy should be strongly discouraged in patients with this diagnosis, and early therapeutic abortion should be considered for those who become pregnant. Anticoagulation throughout gestation, or at least during the third trimester, is recommended. Close hemodynamic monitoring during labor, delivery, and the early postpartum period is advised, and oxygen plus pulmonary vasodilators may be used.
- H. Pregnancy after cardiac transplantation. Pregnancy after cardiac transplantation is considered high risk for the mother and fetus.** Maternal morbidity is increased from hypertension, preeclampsia, renal failure, premature rupture of membranes, and infection. Fetal growth restriction and preterm labor are also a concern, along with potential adverse fetal effects of immunosuppressive medications. One study examined the outcomes of 47 pregnancies in 35 transplant recipients. There was no increase in maternal mortality in this study, but increased maternal morbidity, premature deliveries, and fetal growth restriction were observed.

VIII. MEDICATION CONSIDERATIONS IN PREGNANCY

- A. Cardiovascular drugs.** The most commonly used cardiovascular drug classes and their potential adverse effects during pregnancy are shown in Table 38.7.
- B. Anticoagulation during pregnancy.** Conditions requiring anticoagulation during pregnancy include mechanical prosthetic heart valves, chronic atrial fibrillation, acute venous thromboembolism, Eisenmenger syndrome, antiphospholipid antibody syndrome, and inherited deficiencies predisposing to thromboembolism (e.g., prothrombin gene mutation and factor V Leiden deficiency).

The three most common agents considered for use during pregnancy are **unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), and warfarin.** The Eighth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy has recommended three potential strategies for anticoagulation during pregnancy (Fig. 38.1) and the 2008 ACC/AHA guidelines for the management of patients with valvular heart disease are summarized in Table 38.8.

The choice of anticoagulation regimens depends on the preferences of the patient and physician after consideration of the **maternal and fetal risks associated with the use of each drug.**

- 1. Warfarin.** Warfarin freely crosses the placental barrier and can adversely affect fetal development. It has been associated with a high incidence of spontaneous

TABLE 38.7 Cardiovascular Drugs and Pregnancy

Drug	Indication	FDA category	Potential maternal or fetal side effects
Adenosine	Arrhythmia	C	Limited data on use
Amiodarone	Arrhythmia	D	Hyper/hypothyroidism, IUGR, congenital goiter
ACE-I/ARB	Hypertension	D	Contraindicated, IUGR, oligohydramnios, renal failure, fetal death
Aspirin	Coronary artery disease	D in third trimester	IUGR and bleeding in mother and neonate
β -Blockers	Arrhythmia, hypertension, MI, HOCM, hyperthyroidism, Marfan syndrome, mitral stenosis	C/D	Fetal bradycardia, hypoglycemia, IUGR (atenolol is category D and should be avoided due to greatest IUGR concerns)
Calcium channel blockers	Hypertension	C	Maternal hypotension causing fetal distress reported, potential tocolytic effects
Digoxin	Arrhythmia, heart failure	C	Possible low birth weight, prematurity, but generally considered safe
Dofetilide	Atrial fibrillation	C	Possibly teratogenic in animal studies
Diuretics (thiazides)	Hypertension	B	Hypovolemia and reduced uteroplacental blood flow
Flecainide	Arrhythmia	C	Fetal death; limited data
Hydralazine	Hypertension, heart failure	C	Possible hypospadias, neonatal thrombo-cytopenia, neonatal lupus like syndrome
Lidocaine	Arrhythmia	B	Neonatal CNS depression
Methyldopa	Hypertension	B	Longest safety record, avoid in women with potential for depression
Nitrates	Hypertension	C	Maternal hypotension causing fetal distress reported
Procainamide	Arrhythmia	C	No adverse effects reported in third trimester
Propafenone	Arrhythmia	C	Limited data
Quinidine	Arrhythmia	C	Neonatal thrombocytopenia, mild oxytocic effect
Sodium nitroprusside	Hypertension, aortic dissection	C	Fetal thiocyanate toxicity
Sotalol	Arrhythmia	B/D	Fetal bradycardia, IUGR; category D in second and third trimesters

FDA category: A, controlled studies show no risk; B, no evidence of risk in humans; C, risk cannot be ruled out; D, positive evidence of risk. IUGR, intrauterine growth restriction; ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; MI, myocardial infarction; HOCM, hypertrophic obstructive cardiomyopathy; CNS, central nervous system.

Data retrieved from Micromedex 2.0 correct as of October 1, 2011.

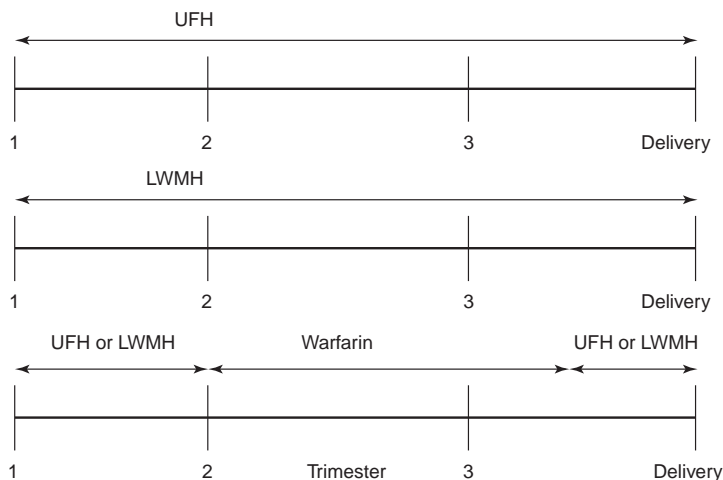


FIGURE 38.1 Anticoagulation options during pregnancy. UFH, unfractionated heparin; LMWH, low-molecular-weight heparin.

TABLE 38.8 ACC/AHA Guidelines for Selection of Anticoagulation Regimen in Pregnant Patients with Mechanical Prosthetic Valves

Class I (benefits >>> risk): procedure/treatment should be performed/administered	Level of evidence
All pregnant patients with mechanical prosthetic valves must receive continuous therapeutic anticoagulation with frequent monitoring	B
For women requiring long-term warfarin therapy who are attempting pregnancy, pregnancy tests should be monitored with discussions about subsequent anticoagulation therapy so that anticoagulation can be continued uninterrupted when pregnancy is achieved	C
Pregnant patients with mechanical prosthetic valves who elect to stop warfarin between weeks 6 and 12 of gestation should receive continuous intravenous UFH, dose-adjusted UFH, or dose-adjusted subcutaneous LMWH	C
For pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose-adjusted subcutaneous UFH, dose-adjusted LMWH, or warfarin should be discussed fully. If continuous intravenous UFH is used, the fetal risk is lower, but the maternal risks of prosthetic valve thrombosis, systemic embolization, infection, osteoporosis, and heparin-induced thrombocytopenia are relatively higher	C
In pregnant patients with mechanical prosthetic valves who receive dose-adjusted LMWH, the LMWH should be administered twice-daily subcutaneously to maintain the anti-Xa level between 0.7 and 1.2 U/mL 4 h after administration	C

(Continued)

TABLE 38.8 ACC/AHA Guidelines for Selection of Anticoagulation Regimen in Pregnant Patients with Mechanical Prosthetic Valves (Continued)

Class I (benefits >>> risk): procedure/treatment should be performed/administered	Level of evidence
In pregnant patients with mechanical prosthetic valves who receive dose-adjusted UFH, the aPTT should be at least twice the control	C
In pregnant patients with mechanical prosthetic valves who receive warfarin, the INR goal should be 3.0 (range 2.5–3.5)	C
In pregnant patients with mechanical prosthetic valves, warfarin should be discontinued and continuous intravenous UFH given starting 2–3 weeks before planned delivery	C
Class IIa (benefits >> risk): it is reasonable to perform procedure/administer treatment	
In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation owing to the high risk of fetal defects	C
In patients with mechanical prosthetic valves, it is reasonable to resume UFH 4–6 h after delivery and begin oral warfarin in the absence of significant bleeding	C
In patients with mechanical prosthetic valves, it is reasonable to give low-dose aspirin (75–100 mg/d) in the second and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin	C
Class III (risk ≥ benefits): procedure/treatment should not be performed/administered	
LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless anti-Xa levels are monitored 4–6 h after administration	C
Dipyridamole should not be used instead of aspirin as an alternative antiplatelet agent in pregnant patients with mechanical prosthetic valves because of its harmful effects on the fetus	B

UFH, unfractionated heparin; LMWH, low-molecular-weight heparin; aPTT, activated partial thromboplastin time; INR, international normalized ratio.

Level of evidence: A, multiple population risk strata evaluated; B, limited population risk strata evaluated; C, very limited population risk strata evaluated.

Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease. *J Am Coll Cardiol*. 2008;52:e1–e142.

abortion, prematurity, still birth, and fetal bleeding. **The incidence of warfarin embryopathy (fetal bone and cartilage formation abnormalities) has been estimated at 4% to 10%; the risk is highest when warfarin is administered during the 6th through the 12th week of gestation.** The risks are dose-dependent, and women maintained on a daily dose of < 5 mg daily have the lowest risks. When administered during the second and third trimesters, warfarin has been associated with fetal central nervous system abnormalities, such as optic

atrophy, microcephaly, intellectual disability, spasticity, and hypotonia. Warfarin's anticoagulant effects are more potent in the fetus than in the mother due to lower fetal levels of the vitamin K–dependent clotting factors and can cause neonatal intracranial hemorrhage or a retroplacental hematoma. Warfarin is considered safe during breast-feeding. Women taking warfarin prior to pregnancy should be counseled regarding the harmful effects, and if pregnancy is contemplated then frequent pregnancy tests or switching to UFH or LMWH should be considered.

2. **Unfractionated heparin.** UFH does not cross the placenta, and unlike warfarin does not have the teratogenic effects, and is, therefore, considered safer. **It is, however, associated with maternal osteoporosis, hemorrhage, thrombocytopenia, or thrombosis (heparin-induced thrombocytopenia with thrombosis [HITT] syndrome), and a high incidence of thromboembolic events with older generation mechanical valves.** UFH may be administered parenterally or subcutaneously throughout pregnancy. Subcutaneous (SC) heparin use in patients with mechanical valve carries an increased risk of valve thrombosis. The appropriate dose of UFH is based on an activated partial thromboplastin time (aPTT) of 2 to 3 times the control level. High doses of UFH are often required to achieve the goal aPTT because of the hypercoagulable state associated with pregnancy. Parenteral infusions should be stopped 4 hours before a cesarean section. In the event of preterm labor, spontaneous hemorrhage, or significant bleeding during delivery, UFH may be reversed with protamine sulfate.
3. **Low-molecular-weight heparin. The use of LMWH during pregnancy remains controversial, as it has not been adequately studied.** Its advantages over UFH include a more predictable anticoagulant response and lower incidences of HITT and osteoporosis. It does not cross the placenta, and it may be safer to the fetus even though data in this regard are limited. A twice-daily dosing schedule should be used. During pregnancy the volume of distribution for LMWH changes, and it is essential to monitor anti-Xa levels. The 4-hour-post dose target anti-Xa level varies between 0.7 to 1.2 and 1.0 to 1.2 U/mL depending on the guidelines followed; the manufacturer's specific target range should also be consulted. Although existing data support the use of LMWH with deep venous thrombosis in pregnancy, the safety and efficacy of LMWH in pregnant patients with mechanical valves remain controversial. One LMWH carries a manufacturer's warning regarding the safety of LMWH in patients with mechanical heart valves, but the true incidence of valve thrombosis in pregnant patients receiving LMWH is unclear. Small studies continue to demonstrate individuals with catastrophic valve thrombosis despite therapeutic anti-Xa levels, further underlining the limitations of the LMWH strategy. However, retrospective auditing of pregnancies managed with LMWH versus warfarin strategies has shown better neonatal outcomes with the LMWH option.
 - (1) Therefore, anticoagulation for mechanical valves during pregnancy is challenging. The choice of anticoagulant should be made after detailed discussion with the patient. Overall, warfarin is probably the safer option for the mother, whereas heparin is less likely to result in fetal harm. In the event of unplanned pregnancy in a patient on warfarin, it is advisable to change from warfarin to UFH or LMWH until 12 weeks and then resume warfarin until the 35th week if the patient is willing to take it, with careful monitoring of the international normalized ratio (INR). The 2011 European Society of Cardiology guidelines on the management of cardiovascular disease during pregnancy offer a class IIaC recommendation for considering continuation of warfarin during the first trimester if the warfarin dose required for therapeutic anticoagulation is < 5 mg/d, after patient information and consent. The ACC/AHA guidelines for selection of anticoagulation regimen in pregnant patients with mechanical prosthetic valves, updated in 2008, are presented in Table 38.8.

- (2) In patients with a **mechanical heart valve with high risk of thrombosis** (first-generation prosthesis; e.g., Starr-Edwards, Björk-Shiley in mitral position, atrial fibrillation, and history of thromboembolism) one of the following algorithms may be used: Continuous IV UFH (aPTT 2.5 to 3.5 times) for 12 to 13 weeks followed by warfarin (INR 2.5 to 3.5 times) for up to 35 weeks followed by IV UFH (aPTT 2.5 to 3.5 times) until delivery **or** SC twice-daily LMWH (anti-Xa level 0.7 to 1.2 U/mL) for 12 to 13 weeks followed by warfarin (INR 2.5 to 3.5 times) for up to 35 weeks followed by IV UFH (aPTT of 2.5 to 3.5 times) or SC twice-daily LMWH (anti-Xa 0.7 to 1.2 U/mL).
- (3) In patients with a **mechanical heart valve with relatively lower risk of thrombosis** (second-generation prosthesis; e.g., St. Jude Medical, Medtronic-Hall, and any mechanical prosthesis in aortic position) options include the following: SC twice-daily LMWH (anti-Xa 0.7 to 1.2 U/mL) or SC twice-daily UFH (aPTT 2.0 to 3.0 times) for 12 to 13 weeks followed by warfarin (INR 2.5 to 3.0 times) for up to 35 weeks followed by IV UFH (aPTT 2.0 to 3.0 times) or SC twice-daily LMWH (anti-Xa 0.7 to 1.2 U/mL) **or** SC twice-daily UFH or SC twice-daily LMWH throughout pregnancy (data supporting this algorithm are limited).

ACKNOWLEDGMENTS: *The authors acknowledge the contributions of Arti Choure, MD, to a previous edition of this chapter.*

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KEY REVIEWS

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Cardiovascular Manifestations of Systemic Disease

Several systemic diseases involve the cardiovascular system, with important therapeutic and prognostic implications. It is vital for cardiologists to recognize, manage, and prevent cardiovascular involvement in various systemic diseases. This chapter reviews the cardiovascular manifestations of various systemic disorders.

I. RHEUMATOLOGIC DISORDERS

A. Rheumatoid arthritis (RA) is one of the commonest forms of chronic inflammatory polyarthritis resulting in joint destruction and deformation. It affects 1% to 3% of the population and is more common in women. It is characterized by chronic symmetrical polyarthritis that typically affects small joints of the hand, such as metacarpophalangeal and proximal interphalangeal joints, in addition to wrists and knees, and spares the thoracolumbar spine and distal interphalangeal joints. The most common cardiovascular manifestations of RA are as follows:

1. **Pericarditis** is very common and can be present in nearly 50% of patients with RA. It can vary from acute pericarditis and chronic asymptomatic effusive pericarditis to cardiac tamponade or chronic constrictive pericarditis, with significant hemodynamic consequences. Most cases with uncomplicated acute pericarditis will respond to nonsteroidal anti-inflammatory drugs (NSAIDs). Corticosteroid therapy may be needed for patients with severe pericarditis. Pericardiocentesis or surgical drainage may be required in cases of tamponade.
2. **Coronary artery disease (CAD)**. Patients with RA have increased mortality compared with the general population and the leading cause of death is cardiovascular disease. Patients with RA have accelerated atherosclerosis, likely a result of chronic systemic inflammation and use of corticosteroids. **After controlling for traditional risk factors of atherosclerosis, patients with RA have been shown to have two to three times greater risk of CAD compared with controls.** In the large prospective Nurses' Health Study, women with RA were found to have a twofold higher risk of myocardial infarction compared with controls. In addition to disease-modifying drugs to reduce systemic inflammation, aggressive lifestyle modification, including tight control of blood pressure and low-density lipoprotein cholesterol, seems warranted.
3. **Cardiomyopathy**. RA can cause granulomatous inflammation of the myocardium leading to cardiomyopathy or involve the conduction system resulting in varying degrees of heart block. Rarely, secondary amyloidosis can occur in RA, leading to an infiltrating cardiomyopathy.
4. **Valvular disease**. A small proportion of patients with RA can have valvular involvement in the form of rheumatoid nodules; however, clinically significant valve disease is very rare.

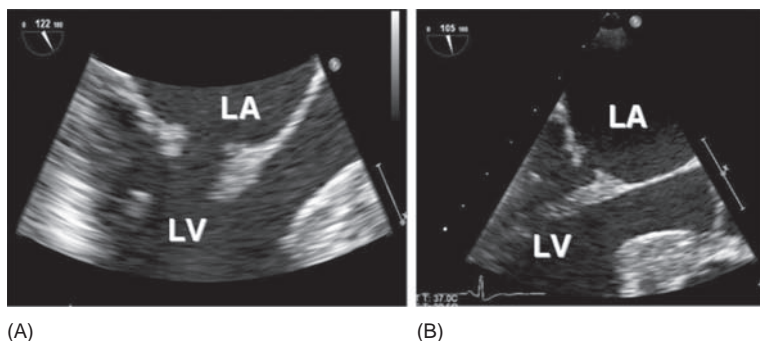


FIGURE 39.1 Transesophageal echocardiogram demonstrating vegetations (Libman-Sacks endocarditis) on the atrial aspect of anterior and posterior mitral valve leaflets in a patient with systemic lupus erythematosus. Panel A is a zoom view of the valve leaflets whereas Panel B shows a less detailed image of the leaflets. LA, left atrium; LV, left ventricle.

B. Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that occurs more commonly in women and is characterized by a wide range of organ involvement, including arthritis, dermatitis, glomerulonephritis, serositis, and hematologic abnormalities. Drug-induced lupus can occur with various cardiac medications, including procainamide, quinidine, and hydralazine, and this is associated with the development of anti-histone antibodies. SLE can affect the cardiovascular system in various ways:

1. **Valvular disease** is the most common type of cardiac involvement in SLE. The characteristic valvular lesions in SLE are nonmobile, noninfectious vegetations on the atrial aspect of the mitral valve or the arterial aspect of the aortic valve, referred to as Libman-Sacks endocarditis (Fig. 39.1). Studies have shown that valvular involvement is very common in SLE and occurs in > 50% of patients. The most common valvular abnormality is valvular thickening, followed by vegetations and valvular regurgitation or stenosis. Serial echocardiography should be performed to monitor for progression of valve disease. The vegetations can embolize and cause stroke or myocardial infarction in rare cases.
2. **Pericarditis** is very common in SLE and has been shown to occur in > 50% to 60% of patients. Associated pericardial effusion is usually exudative, with elevated protein and low glucose concentration, and infection must be ruled out in the setting of concomitant immunosuppressive therapy. Cardiac tamponade and chronic constrictive pericarditis can also occur.
3. **Coronary artery disease.** Premature coronary atherosclerosis has been shown to occur commonly in patients with SLE compared with age-matched controls. CAD can also manifest as coronary arteritis, thrombosis in the presence of antiphospholipid antibody syndrome (APLA—see Section 1.C) or, rarely, embolism from Libman-Sacks endocarditis.
4. **Myocardial dysfunction** in patients with SLE can result from ischemia, valve disease, or long-standing hypertension. Patients with peripheral skeletal myositis have an increased risk of lupus myocarditis.
5. **Conduction system disease** with complete heart block can occur in infants born to mothers with SLE, particularly those with anti-Ro and anti-La antibodies. Women with SLE contemplating pregnancy should undergo screening for these antibodies prior to pregnancy and, if present, should undergo fetal echocardiography to screen for conduction abnormalities and myocardial dysfunction. There is some evidence suggesting a role for intrauterine dexamethasone in reversing fetal myocarditis and slowing conduction disease.

- C. Antiphospholipid antibody syndrome** is characterized by the presence of antiphospholipid antibodies or lupus anticoagulant, recurrent venous or arterial thrombosis, and miscarriages. APLAs can occur independently, referred to as primary APLAs, or can be associated with other autoimmune diseases such as SLE (10% to 30%) and are then referred to as secondary APLAs. Valvular disease is common in APLAs and is characterized by noninfectious vegetations similar to those seen in SLE (Libman-Sacks endocarditis). Management of arterial or venous thrombosis or significant valvular vegetations includes anticoagulation therapy with warfarin. Monitoring anticoagulant effect while on heparin or warfarin may be difficult, as these patients can have prolonged partial thromboplastin time or international normalized ratio at baseline, in which case monitoring of anticoagulant effect can be done using activity levels of factors II and X.
- D. Scleroderma** or systemic sclerosis is a rare autoimmune disorder, characterized by vasospasm, microvascular occlusion, and fibrosis of skin and multiple organs. Diffuse or progressive systemic sclerosis (PSS) results in widespread cutaneous and visceral involvement. Limited scleroderma, also known as CREST syndrome, is characterized by calcinosis cutis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia. Cardiovascular involvement can occur in progressive as well as limited scleroderma.
- 1. Pericardial disease** in the form of fibrinous pericarditis is present in over 70% of patients on autopsy studies, though it is clinically manifest as symptomatic pericarditis in only about 15% to 30% of patients. Small pericardial effusions can be detected in about 40% of patients by echocardiography, but are rarely significant. Acute pericarditis may be treated with NSAIDs, with close monitoring of renal function. Corticosteroids carry the risk of inducing scleroderma renal crisis.
 - 2. Pulmonary hypertension (PH)** is responsible for significant morbidity and mortality in patients with scleroderma and is more common in the limited type. Autopsy studies have shown histopathological changes consistent with PH in 65% to 80% of patients with scleroderma; however, < 10% of patients manifest PH clinically. Patients with scleroderma and PH appear to have a worse prognosis compared with those with primary PH, with a 2-year survival of < 50%. Drugs for PH, such as prostacyclins (epoprostenol, treprostinil, and iloprost), endothelin receptor antagonists (bosentan and ambrisentan), and phosphodiesterase inhibitors (sildenafil and tadalafil), have been studied in patients with scleroderma and PH. Some of these studies have demonstrated improvement in the 6-minute walk test, exercise capacity, and cardiopulmonary hemodynamics; however, no improvement in mortality has been demonstrated. Echocardiography should be used to screen for asymptomatic PH.
 - 3. Scleroderma renal crisis** is defined as the new onset of accelerated hypertension or rapidly progressive oliguric renal failure during the course of systemic sclerosis. It is usually associated with rising creatinine, thrombocytopenia, microangiopathy, and signs and symptoms of congestive heart failure. Scleroderma renal crisis occurs in about 10% of patients with scleroderma and is more common in the diffuse form of the disease. Angiotensin-converting enzyme inhibitors are the mainstay of therapy.
 - 4. Myocardial involvement** with patchy fibrosis can occur in patients with scleroderma. Epicardial coronary arteries are usually normal on angiography; however, ischemia can occur secondary to microvascular vasospasm. Diastolic dysfunction has been commonly found in these patients. Electrical abnormalities such as frequent ectopy, supraventricular arrhythmias, and nonsustained ventricular tachycardia (VT) can occur in patients with PSS. The risk of sudden cardiac death is higher in those with a history of syncope.
- E. Seronegative spondyloarthropathies** include HLA-B27 antigen-associated arthropathies such as ankylosing spondylitis, reactive arthritis, psoriatic arthritis, and inflammatory bowel disease-associated arthritis. These disorders are characterized by

involvement of the spine and sacroiliac joints and inflammation of tendons, ligaments, and their insertion points into bones (enthesitis). In contrast to RA and SLE, these disorders occur more commonly in males. Ankylosing spondylitis results in ankylosis, sacroiliitis, and asymmetric peripheral arthritis. Reactive arthritis is characterized by conjunctivitis, genital ulcers, and asymmetric peripheral arthritis. Proximal aortitis with or without aortic regurgitation and conduction disturbances are most commonly associated with ankylosing spondylitis and reactive arthritis. **Proximal aortitis can lead to thickening, stiffness, and dilatation of the aortic root with aortic regurgitation.** Aortic or mitral valve thickening with nodularities of the aortic cusps and thickening of the anterior mitral valve leaflet resulting in a characteristic subaortic bump are commonly observed valvular abnormalities in patients with ankylosing spondylitis. Extension of the subaortic inflammation and fibrotic process into the basal septum can result in conduction abnormalities such as heart block, which is usually at the level of the atrioventricular (AV) node. Other less common cardiac abnormalities include pericarditis, diastolic dysfunction, and supraventricular arrhythmias.

- F. Dermatomyositis (DM) and polymyositis (PM)** are idiopathic inflammatory myopathies characterized by proximal skeletal muscle weakness and elevated levels of muscle enzymes, such as creatine kinase and aldolase. DM is characterized, in addition, by skin involvement such as erythematous scales on the knuckles (Gottron's papules), knees, and elbows, and periorbital swelling and violaceous rash around the eyelids (heliotrope rash). DM can be part of a paraneoplastic syndrome, particularly in the elderly. Cardiovascular manifestations of DM and PM include pericarditis, conduction abnormalities, and congestive heart failure secondary to myocarditis that can be focal or generalized and may be steroid responsive. Cardiac magnetic resonance imaging (MRI) with delayed gadolinium enhancement may be useful in monitoring response to therapy. Coronary vasculitis is a rare manifestation. The differentials for muscle weakness include the following: corticosteroid myopathy, which generally affects skeletal muscle but not cardiac or respiratory muscle and is associated with a normal creatine kinase, and statin myopathy, which can be differentiated based on history of statin use and myalgias or with electromyography and biopsy if needed. Management of DM and PM includes corticosteroids, and adjunctive therapies include methotrexate, azathioprine, and intravenous immunoglobulin (IVIg).

II. SYSTEMIC VASCULITIDES

- A. Giant cell arteritis (GCA)**, also referred to as temporal arteritis, is the most common vasculitis in patients older than 50 years. It is more prevalent in women compared with men and in those of Northern European descent. GCA usually affects the extracranial branches of the aorta, sparing the intracranial vessels. Transmural inflammation of the vessels is followed by intimal hyperplasia, luminal occlusion, and end-organ ischemia. Branches of the external and internal carotid arteries are particularly susceptible, and the typical clinical presentation of GCA includes new-onset headache, scalp and temporal artery tenderness, jaw pain, acute visual loss, and polymyalgia rheumatica. Concomitant elevation in erythrocyte sedimentation rate (ESR) is almost always present. **Temporal artery biopsy is the gold standard for diagnosis and shows transmural chronic granulomatous inflammation with destruction of elastic laminae.** Treatment with corticosteroids should be initiated as soon as possible, without waiting for temporal artery biopsy. GCA is associated with thoracic and abdominal aortic aneurysms. According to one study, patients with GCA are 17 times more likely to develop thoracic aortic aneurysm and 2.4 times more likely to develop abdominal aortic aneurysm compared with age-matched controls. Rare cardiovascular manifestations include pericarditis, myocarditis, and coronary vasculitis. Studies have shown that MRI or fluorine-18-deoxyglucose positron emission tomography (FDG PET) can be useful for the detection of large vessel vasculitis. Transthoracic echocardiography and abdominal ultrasonography are useful in screening for thoracic and



FIGURE 39.2 Magnetic resonance angiogram in a patient with Takayasu arteritis demonstrating severe diffuse narrowing of both common carotid arteries and severe disease in the left subclavian artery (arrows).

abdominal aortic aneurysms. As mentioned, corticosteroids are the agents of choice in patients with GCA. Low-dose aspirin should be added, since it has been shown to reduce the rate of blindness and stroke in patients with GCA.

- B. Takayasu arteritis (TA)** is also a large vessel vasculitis like GCA, but it occurs in young women, particularly of Indian, Japanese, and African-American descent. It typically affects the aorta and its major branches (Fig. 39.2). In TA, arterial stenoses are more common than aneurysms. Clinically, TA is characterized by claudication (upper extremities more common compared with lower extremities), “pulselessness” or asymmetric pulses, and blood pressures. Systemic symptoms such as fever, malaise, arthralgias, myalgias, night sweats, and elevated ESR may indicate active disease. Renal artery stenosis can be associated with hypertension. Cardiac manifestations include aortic regurgitation secondary to aortic root dilatation and rarely coronary arteritis. Diagnosis is based on imaging studies that show vascular involvement typical of TA. Imaging modalities such as MRI and PET enable visualization of inflammation in the vessel wall. Therapeutic strategies include corticosteroids, immunosuppressants such as cyclophosphamide or methotrexate in steroid-resistant cases, and anatomic correction using an endovascular or surgical approach when feasible.
- C. Kawasaki disease** is an acute febrile illness that affects children, usually below the age of 5 years, with the highest incidence in those of Asian descent. Diagnosis is made largely on clinical grounds based on the following criteria: (1) fever ≥ 5 days; (2) conjunctival injection; (3) oropharyngeal changes including erythema, swelling and fissuring of the lips, diffuse erythema of the oropharynx or strawberry tongue; (4) extremity changes such as erythema of palms and soles, induration of hands and feet, desquamation of the skin of hands and feet; (5) polymorphous rash; and (6) cervical lymphadenopathy, usually a single node > 1.5 cm. Fever and four out of five remaining criteria must be present for a definitive diagnosis. Cardiovascular manifestations include pericarditis, myocarditis, aortitis, aortic regurgitation, and arrhythmias. Coronary vasculitis can occur, which if left untreated can lead to

coronary aneurysm formation in about 4 weeks. Aneurysms larger than 8 mm are referred to as giant aneurysms, and these can thrombose acutely, leading to myocardial infarction as well as sudden death. Treatment with aspirin and single-dose IVIg (dose 2 g/kg) reduces the formation and progression of coronary aneurysms. Recommendations by the American Heart Association include long-term follow-up and consideration of anticoagulation for children with multiple giant coronary aneurysms or known obstructive lesions, chronic low-dose aspirin therapy, and coronary artery bypass or percutaneous intervention if lesions are severe and symptomatic.

- D. Idiopathic aortitis** is commonly associated with disorders such as TA and GCA in addition to rheumatologic diseases such as SLE, Behçet's disease, seronegative spondyloarthropathies, antineutrophil cytoplasmic antibody–associated vasculitides, Cogan syndrome, and sarcoidosis. Although most cases of aortitis are noninfectious in etiology, infectious causative agents such as staphylococcus, streptococcus, salmonella, and syphilis must be considered. Aortitis can be diagnosed for the first time in surgically excised specimens after aortic surgery. In a 20-year review of over 1,200 aortic surgical specimens at Cleveland Clinic, 52 (4.3%) were clinically and pathologically classified as idiopathic aortitis. Of these, 67% were women. In 96% of cases with idiopathic aortitis and aneurysm formation, aortitis was limited to the thoracic aorta. In 96% of cases, signs of systemic illness were not present at the time of aortic surgery. In 31% (16 of 52), aortitis was associated with a remote history of vasculitis and a variety of other systemic disorders such as GCA, TA, SLE, and Wegener's. Over a mean follow-up of 41 months, new aneurysms were found in 6 out of 25 patients not treated with corticosteroids. It is prudent to follow these patients with serial imaging to identify new aneurysms. Treatment with corticosteroids requires evidence of an ongoing systemic inflammatory disease.
- E. Churg-Strauss syndrome (CSS)** is a rare small vessel vasculitis characterized by asthma, peripheral eosinophilia, pulmonary infiltrates, and varying degrees of cutaneous, renal, neurologic, and cardiac involvement. Histopathologically, it is characterized by eosinophilic granulomatous inflammation of small vessels of the involved organ. Cardiovascular manifestations are common in CSS and are responsible for significant morbidity and mortality in these patients. The most common cause of death is congestive heart failure secondary to cardiomyopathy, the cause of which may be small vessel vasculitis or eosinophilic infiltration of the myocardium followed by fibrosis or a combination of both pathologic processes. Other cardiac manifestations include myocarditis and pericarditis with or without pericardial effusion. Therapy mainly includes corticosteroids but other immunosuppressants may be needed.
- F. Polyarteritis nodosa (PAN)** is a rare nongranulomatous disease affecting medium-sized arteries that leads to weakening of the vessel wall secondary to necrotizing changes with aneurysm formation or intimal proliferation and stenosis. It is a systemic disease characterized by painful subcutaneous nodules, digital infarcts, mononeuritis multiplex, renal infarction and renal failure, hypertension, and pulmonary infarction. Cardiac manifestations include angina, myocardial infarction, congestive heart failure, and arrhythmias such as supraventricular tachycardia. Treatment is similar to CSS and primarily includes corticosteroids.

III. CONNECTIVE TISSUE DISEASES

- A. Marfan syndrome** was first described over 100 years ago by Antoine-Bernard Marfan, a French pediatrician. It is an autosomal dominant connective tissue disease secondary to mutations in the fibrillin-1 gene (*FBNI*) that encodes major constituent proteins of microfibrils, which form a significant component of the extracellular matrix. It is a common heritable condition with an estimated prevalence of 1 per 3,000 to 5,000 individuals. About 25% cases have no family history and are a result of de novo mutations. Marfan syndrome is characterized by disproportionate long bone overgrowth with long extremities and tall stature, joint hypermobility,

high-arched palate, and ectopia lentis. In addition, patients with Marfan syndrome can have pectus excavatum or carinatum, scoliosis, arachnodactyly, erosion of lumbar vertebrae from dural ectasia, apical pulmonary blebs with spontaneous pneumothorax, myopia, retinal degeneration, and cataracts. The diagnosis of Marfan syndrome is based on the Ghent criteria, based on consensus by an international expert panel, which have been revised recently with more weight on cardiovascular manifestations. In the absence of family history, the presence of aortic root aneurysm or aortic dissection and ectopia lentis establishes the diagnosis of Marfan syndrome. In the absence of either of these two, the presence of *FBNI* gene mutation or a combination of systemic manifestations listed above is required. Cardiovascular manifestations of the Marfan syndrome are as follows:

- 1. Aortic aneurysm and dissection.** Defect in microfibrils results in degeneration of elastic fibers in the aortic media (sometimes inappropriately referred as “cystic medial necrosis”), with resultant aortic aneurysm formation. This typically occurs at the level of the aortic root and involves the sinuses of Valsalva. The aortic root diameter should be serially monitored with echocardiography or computed tomography/MRI. According to the current guidelines, annual imaging is recommended if stability in aortic root size is documented. If the baseline aortic diameter is > 4.5 cm or if there is significant growth from baseline, more frequent imaging should be considered. Elective surgical repair for aortic root aneurysm is usually performed at a threshold of 5 cm or greater in patients with Marfan syndrome. This threshold is smaller than for other disorders with aortic aneurysm, given the greater tendency for aortic dissection at smaller diameters in patients with Marfan syndrome. Indications for earlier repair at sizes < 5.0 cm include: rapid growth defined as > 0.5 cm/year, family history of aortic dissection at a diameter < 5.0 cm or the presence of significant aortic regurgitation. Aortic regurgitation usually occurs secondary to aortic root dilatation. Aortic dissection in Marfan syndrome is usually type A, i.e., starts in the ascending aorta and can extend to a variable degree distally. About 10% of dissections in Marfan syndrome begin distal to the origin of the left subclavian artery (type B). Type A dissection necessitates immediate repair, given the high risk of life-threatening complications if not treated promptly. Medical management in patients with Marfan syndrome includes β -blockers, which have been shown to reduce the risk of aortic dilatation and aortic dissection. The beneficial effect of β -blockers is largely due to the reduction in heart rate and the rate of pressure increase in the aorta, which leads to less stress on the aortic wall. Recently, angiotensin receptor blockade with Losartan was shown to slow the rate of aortic root dilatation in patients with Marfan syndrome, secondary to mitigation of excessive transforming growth factor beta signaling. Due to the risk of acute aortic dissection, patients with Marfan syndrome should be counseled to avoid isometric exercise, including heavy weight lifting, contact sports, and competitive athletics. Females of childbearing age with Marfan syndrome should be counseled regarding the high risk of transmission of their disease to the child. Enlargement of the aortic root to > 4.0 cm increases the risk of aortic dissection, particularly during the third trimester, parturition, and first few months postpartum. If the aortic root is < 4 cm, then the risk of dissection is considered low, and pregnancy can be allowed with β -blocker therapy and careful monitoring with serial echocardiography throughout pregnancy.
- 2. Mitral valve prolapse** commonly occurs in patients with Marfan syndrome and is more common in women. The incidence is as high as 60% to 80%, and progressive mitral regurgitation occurs in about 25% of patients. The valve leaflets are usually thickened and redundant and occasionally ruptured chordae or prolapse may be present. Progressive untreated mitral regurgitation can lead to left ventricular dilatation, congestive heart failure, and PH. Tricuspid valve

prolapse can occur concomitantly. Standard management for chronic severe mitral regurgitation is indicated in symptomatic patients, with repair of the mitral apparatus if possible, but replacement may be necessary when the leaflets are very redundant or there is severe annular calcification or chordal damage.

3. **Dilated cardiomyopathy** independent of, or out of proportion to, valvular abnormalities can occur in patients with Marfan syndrome. This has been hypothesized to be secondary to a potential role of fibrillin mutations in the reduction of myocardial function.
 4. **Arrhythmias**, both supraventricular and ventricular, can occur in patients with Marfan syndrome.
- B. Loeys-Dietz syndrome (LDS)** is a recently recognized autosomal dominant connective tissue disease with similarities to the Marfan syndrome but with important genotypic and phenotypic differences. It is caused by mutations in the genes encoding transforming growth factor beta receptors 1 and 2 (*TGFBR1* and *TGFBR2*). Type I LDS is characterized by arterial tortuosity and aneurysms, most often in the aortic root but can involve other arteries, hypertelorism (widely spaced eyes), and bifid uvula or cleft palate or both. Patients with type II LDS are characterized by cutaneous manifestations such as velvety translucent skin, easy bruising, atrophic scars, and joint laxity, similar to vascular Ehlers-Danlos syndrome. Patients with LDS do not have ectopia lentis. They are, however, predisposed to more aggressive and widespread vascular disease, including aneurysm formation and dissection, compared with Marfan syndrome, with a mean age of death of 26 years. Patients with LDS can develop aortic dissection at aortic diameters < 5 cm; hence, elective repair is recommended at much smaller aortic root dimensions (4.0 cm) compared with Marfan syndrome. Surgical repair has not been associated with tissue fragility in patients with LDS. More than 50% of patients with LDS can develop aneurysms of other vessels; hence, yearly surveillance imaging of the entire vascular tree has been recommended.
- C. Ehlers-Danlos syndrome, type IV or vascular form**, is a rare autosomal dominant disorder associated with mutations in the gene for type III procollagen (*COL3A1*). It is characterized by easy bruising, thin skin with visible veins, characteristic facial features, and rupture of arteries, uterus, or intestines. Arterial rupture or dissections are the major causes of mortality in these patients and can occur in the thoracic or abdominal vessels, including aortic rupture or dissection. The median age of survival was about 48 years in a study of 220 patients with this disorder. In the same study, 25% of patients had a medical or surgical complication by the age of 25 years and > 80% had such complications by the age of 40 years. In contrast to LDS, tissues are friable in Ehlers-Danlos syndrome, and surgical repair after ruptured aneurysm or dissection can be complicated by hemorrhage or poor wound healing. The role of prophylactic surgical repair for unruptured aneurysms is unclear. Pregnant women have a 50% chance of transmitting the disorder to the child, and about 11.5% risk of mortality. Pregnancy should be considered high risk and women should be counseled against it.

IV. OTHER SYSTEMIC DISEASES

- A. Sarcoidosis** is an idiopathic systemic granulomatous inflammatory disease affecting mainly the lungs, but can involve the lymph nodes, skin, eyes, heart, kidneys, musculoskeletal system, nervous system, and endocrine system. Histopathologically, it is characterized by the presence of noncaseating granulomas. It is more common in young and middle-aged adults (peak incidence second to fourth decades) and in African-Americans. Cardiac involvement is found in 25% of patients with sarcoidosis on autopsy, but only 5% of patients have clinically apparent cardiac involvement. The most common sites of cardiac involvement are the basal interventricular septum, AV node and the His bundle, focal regions in the ventricular free walls, and the papillary muscles. Cardiovascular manifestations of sarcoidosis are as follows:
1. **Arrhythmias** can vary from conduction disturbances, including heart block to fatal ventricular arrhythmias. Complete heart block is the most common abnormality in

patients with clinically evident sarcoidosis and is found in 20% to 30% of patients. First-degree heart block and bundle branch blocks are also seen. Granulomatous infiltration of the ventricular myocardium can set up foci of automaticity, leading to ventricular arrhythmias. VT is the most common arrhythmia and is reported in about 20% of patients with sarcoidosis. Sudden cardiac death caused by an arrhythmia is one of the leading causes of death (> 60%) in patients with sarcoidosis.

2. **Congestive heart failure** may occur, secondary to widespread infiltration of the myocardium. It may also occur due to arrhythmias, cor pulmonale from long-standing PH, valvular abnormalities, or a combination of these abnormalities. Progressive congestive heart failure is the second most common cause of death in patients with sarcoidosis.
3. **Pericardial** involvement can manifest as pericarditis, pericardial effusion, and constrictive pericarditis.

Diagnosis of cardiac sarcoidosis may be difficult. Endomyocardial biopsy with noncaseating granulomas has high specificity, but poor sensitivity owing to the patchy nature of myocardial involvement particularly in the basal septum, whereas the location of biopsy is often the apical septum. Electrocardiogram often reveals conduction abnormalities but has poor sensitivity. Echocardiographic findings include increased ventricular septal thickness (secondary to granulomatous expansion) or wall thinning (due to fibrosis), aneurysms, regional wall motion abnormalities, and eventually ventricular dilatation. Contrast-enhanced MRI and 18-FDG PET are more sensitive modalities for detecting early cardiac involvement and findings correlate with disease severity. These imaging modalities can be used in evaluating response to therapy. Corticosteroid therapy can halt cardiac disease progression and improve survival; however, it does not prevent sudden cardiac death. Pacemaker implantation is often necessary in cases of symptomatic heart block or asymptomatic high-grade conduction disease. Implantable cardioverter defibrillator implantation is recommended for primary prevention in patients with cardiac sarcoidosis at risk for sudden cardiac death, such as those with a history of nonsustained VT or low ejection fraction. Cardiac transplantation for cardiac sarcoidosis is rarely used, as the disease can recur in the transplanted heart. However, it may be considered in young patients with severe end-stage heart failure or resistant VT.

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CHAPTER

40

Arun Dahiya

Pericardial Disease

- I. **INTRODUCTION.** The pericardium is a fibrous sac composed of two layers. The inner monocellular visceral layer is composed of mesothelial cells and is adherent to the myocardium. The outer parietal layer is a fibrous layer < 2 mm thick that consists mostly of collagen and elastin. It is joined to adjacent intrathoracic structures by means of ligaments. Interspersed between the two layers is a small amount of serous pericardial fluid, generally about 15 to 35 mL. **The normal pericardium is distensible and permits unimpeded expansion of the ventricles during diastole. Normally, changes in intrathoracic pressure are easily transmitted to the heart,** resulting in increased venous return to the right side of the heart with inspiration and increased pulmonary venous return to the left side of the heart with expiration.

The pericardium helps to maintain the position of the heart within the chest cavity, acts to reduce friction during the cardiac cycle, and also acts as a barrier to infection and inflammation. The pericardium secretes prostaglandins that can modulate cardiac reflexes and coronary tone.

- A. Acute pericarditis is a clinical syndrome caused by **inflammation of the pericardium**, and it is associated with **chest pain, a friction rub, and characteristic electrocardiographic changes**. The incidence of acute pericarditis is 2% to 6% in autopsy series, although it is diagnosed clinically in only 1 in 1,000 admissions. It is more **common in adults (20 to 50 years of age) and in men**.
 - B. Constrictive pericarditis is caused by **fibrous thickening of the pericardium** secondary to **chronic inflammation** from a variety of causes.
 - C. Pericardial effusion is a **fluid collection in the pericardial space**. The clinical presentation may range from being **asymptomatic to life-threatening** hemodynamic compromise, depending on the **underlying cause of the effusion** and the **rate of accumulation**, as discussed later in detail.
 - D. Cardiac tamponade is a clinical emergency that arises when a pericardial fluid collection impairs diastolic filling sufficiently to produce a low cardiac output state.
- II. ACUTE PERICARDITIS.** There are a large number of potential etiologies of acute pericarditis. In practice, these are classified into the following groups: idiopathic, infectious, inflammatory, uremic, post-myocardial infarction (post-MI), neoplastic, and traumatic (Table 40.1).
- A. Etiology**
- 1. **Idiopathic.** Most cases of acute pericarditis are **idiopathic**, although many of these may be **viral in origin**.

TABLE 40.1 Causes of Pericarditis**Idiopathic (nonspecific)**

Viral infections: coxsackievirus A, coxsackievirus B, echovirus, adenovirus, mumps virus, infectious mononucleosis, varicella, hepatitis B virus, and acquired immunodeficiency syndrome

Bacterial infections: *Pneumococcus*, *Staphylococcus*, *Streptococcus*, gram-negative septicemia, *Neisseria meningitidis*, *Neisseria gonorrhoeae*, tularemia, *Legionella pneumophila*, and *Mycobacterium tuberculosis*

Fungal infections: histoplasmosis, coccidioidomycosis, *Candida*, and blastomycosis

Uremia

Neoplasm: lung cancer, breast cancer, leukemia, Hodgkin's disease, and lymphoma

Radiation

Autoimmune diseases: acute rheumatic fever, systemic lupus erythematosus, rheumatoid arthritis, scleroderma, mixed connective tissue disease, Wegener's granulomatosis, and polyarteritis nodosa

Inflammatory disease: sarcoidosis, amyloidosis, inflammatory bowel disease, Whipple's disease, and temporal arteritis

Drugs

Hydralazine, procainamide, phenytoin, isoniazid, phenylbutazone, doxorubicin, and penicillin

Trauma

Postmyocardial-pericardial injury syndromes: postmyocardial infarction syndrome (Dressler's syndrome) and postpericardiotomy syndrome

Dissecting aortic aneurysm

2. **Viral pericarditis.** The most commonly involved viruses are coxsackievirus B and echovirus. A **prodrome of upper respiratory tract symptoms** preceding the onset of chest pain, along **with a fourfold or higher rise in viral convalescent antibody titers**, supports the diagnosis. Most cases are self-limited; infrequent complications include myocarditis (i.e., myopericarditis), recurrent pericarditis, pericardial effusion, tamponade, and constrictive pericarditis.
 3. **Purulent pericarditis.** Purulent pericarditis usually occurs as a **complication of pneumonia or empyema** caused by staphylococci, pneumococci, or other streptococci. Early diagnosis of purulent pericarditis is paramount, as **cardiac tamponade often develops and is associated with high mortality. Purulent pericarditis** is characterized by **acute onset of fever, shaking chills, night sweats, and dyspnea** of a few days duration. **Chest pain or pericardial friction rub is not necessarily present.**
 4. **Tuberculous pericarditis.** Although uncommon in the United States, this entity should be considered in patients with fever and pericardial effusion, particularly if there is an underlying immunocompromised state. Pericardial involvement occurs in 1% to 2% of cases of pulmonary tuberculosis. **If the clinical suspicion is high, the patient should be hospitalized and started on triple drug therapy**, while definitive diagnostic testing is undertaken (acid-fast bacilli [AFB] testing and pericardial/pleural biopsy).
 5. Post-MI pericarditis occurs most often after a large anterior wall MI. Because post-MI pericarditis is a marker for extensive myocardial necrosis, these **patients are at an increased risk for congestive heart failure and mortality at 1 year after MI**. It is notable that the rate of post-MI pericarditis has declined since the introduction of successful reperfusion therapies.
 6. **Dressler's syndrome** usually **occurs weeks to several months after MI**, with an incidence of about 1%. It presents as **malaise, fatigue, and chest pain** that can be of concern for recurrent MI. The cause of Dressler's syndrome is unclear, although it has been proposed to be autoimmune in nature.
 7. **Postpericardiotomy syndrome.** Although similar to Dressler's syndrome in presentation, it **usually occurs within the first 6 to 8 weeks following cardiac surgery**. The incidence varies from 10% to 40%, and the syndrome is believed to be caused by an autoimmune reaction.
 8. Uremic pericarditis typically develops in patients who are just beginning renal replacement therapy with hemodialysis. The majority present with a **rub**, and the associated **pericardial effusions tend to be large**. The cause is unknown but does not seem to be related to the level of circulating uremic catabolites or toxins.
 9. **Neoplastic pericarditis.** Tumors involving the pericardium are typically metastatic in nature (lung, breast, Hodgkin's and non-Hodgkin's lymphoma, and leukemia). It is important to **suspect cardiac tamponade in patients with a known malignancy who present with symptoms of relatively acute onset fatigue, dyspnea, or edema**.
 10. **Autoimmune and inflammatory.** Lupus, rheumatoid arthritis, vasculitis, and other rheumatologic disorders are also associated with pericarditis.
- B. Clinical presentation**
1. **Signs and symptoms**
 - a. Chest pain from pericarditis is described as a severe, sharp retrosternal pain that may radiate to the neck, shoulders, and back, worsening when lying supine, coughing, or during inspiration. The pain may be alleviated when the patient leans forward.
 - b. There may be a **prodrome of fever and myalgias**.
 - c. Dyspnea may result from shallow breathing due to inspiratory chest pain.
 - d. Patients with **purulent pericarditis** may appear toxic with **high fevers, shaking chills, and night sweats**.

- e. Tuberculous pericarditis is characterized by gradual onset of symptoms with chronic, nonspecific, constitutional symptoms such as **fever, chills, and night sweats**.
- 2. **Physical findings**
 - a. The **pericardial friction rub is the major clinical finding in pericarditis**, but it is not present in all cases. It is described as a **scratchy, grating, and high-pitched sound**. The rub is often evanescent, changes in quality and intensity on serial examinations, and may be accentuated with deep respiration. Classically, it has **three components**, corresponding to atrial systole, ventricular systole, and early ventricular diastole. Most often, however, it is a **biphasic rub** consisting of the atrial and ventricular systolic components.
 - b. **Auscultation of the rub is ideally performed** using the diaphragm of the stethoscope **at the left lower sternal border** during inspiration, with the patient leaning forward.
- C. **Laboratory examination and diagnostic testing.** Pericarditis is a **clinical diagnosis based on history, physical examination, chest radiograph, and serial electrocardiographic changes**. Based on the clinical scenario, some patients may require further testing, such as tuberculin skin testing, fungal tests, viral serologies, cold agglutinins, thyroid function tests, heterophile antibodies, antinuclear antibodies, rheumatoid factor, bacterial culture, and cytology.
- 1. **Electrocardiography.** The associated electrocardiographic changes evolve through **four stages** (Table 40.2). Although these changes occur in most patients, their **absence does not exclude acute pericarditis**, particularly in patients with neoplastic or tuberculous pericarditis.
 - a. The first stage usually occurs within hours of the onset of chest pain and is diagnostic of acute pericarditis (Fig. 40.1). The presence of **stage 1 electrocardiographic changes is most useful in confirming the diagnosis of acute pericarditis**, yet such changes are often **difficult to distinguish from changes associated with early repolarization and acute infarction**. There is **diffuse ST-segment elevation with upright T waves** in all leads

TABLE 40.2 Typical Electrocardiographic Evolution of Acute Pericarditis

Stage	J-ST	T waves	PR segment
“Epicardial” leads (I, II, aVL, aVF, and V₃–V₆)			
I	Elevated	Upright	Depressed or isoelectric
II (early)	Isoelectric	Upright	Isoelectric or depressed
II (late)	Isoelectric	Low to flat to inverted	Isoelectric or depressed
III	Isoelectric	Inverted	Isoelectric
IV	Isoelectric	Upright	Isoelectric
“Endocardial” leads (aVR, often V1, and sometimes V2)			
I	Depressed	Inverted	Elevated or isoelectric
II (early)	Isoelectric	Inverted	Isoelectric or elevated
II (late)	Isoelectric	Shallow to flat to upright	Isoelectric to elevated
III	Isoelectric	Upright	Isoelectric
IV	Isoelectric	Inverted	Isoelectric

Modified from Spodick DH. Electrocardiographic changes in acute pericarditis. *Am J Cardiol*. 1974;33:470.

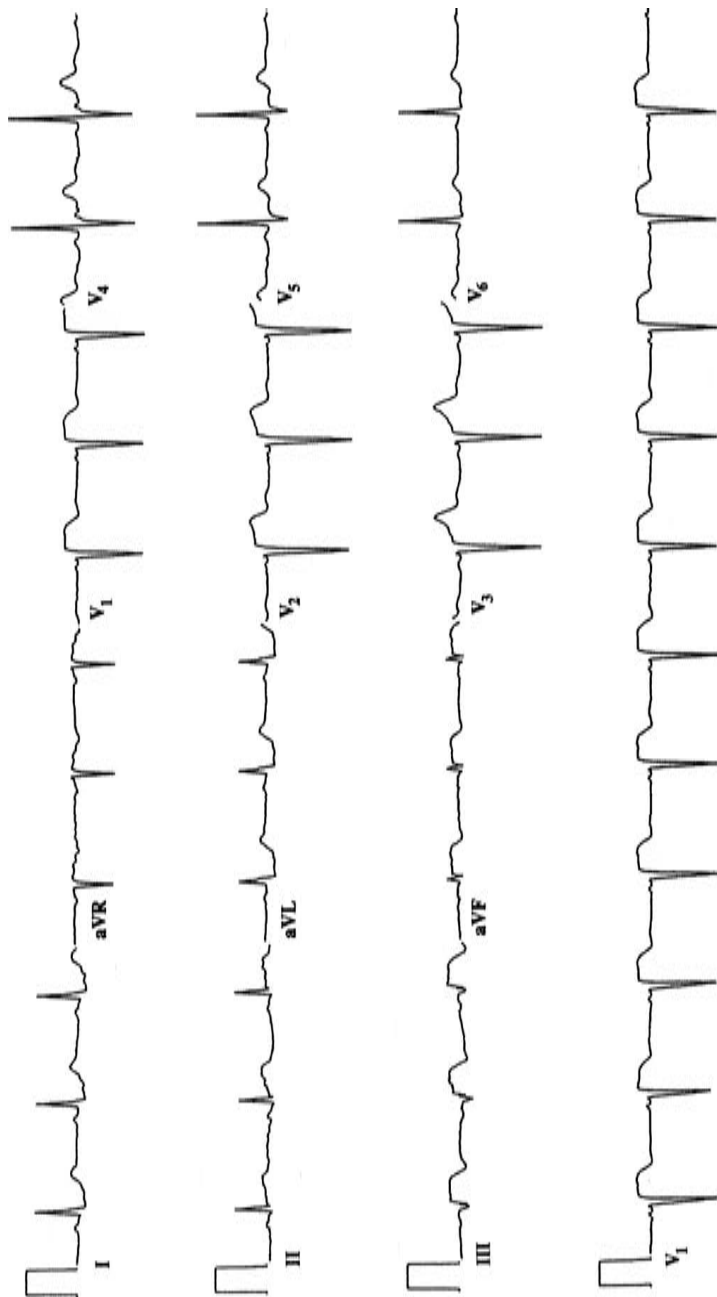


FIGURE 40.1 Stage 1 electrocardiographic changes in acute pericarditis. Note PR segment elevation in lead aVR, and diffuse ST elevation and the upsloping nature of ST segments as compared with acute myocardial infarction.

except aVR and V₁, **PR-segment depression** is seen in all leads except aVR and V₁. There is often PR-segment elevation in lead aVR (the “knuckle” sign).

- b. Stage 2, which occurs several days later, is characterized by resolution of PR/ST segments to baseline and T-wave flattening.
 - c. The T-wave inversions mark **stage 3**.
 - d. Stage 4 occurs when T waves become upright again, which may take days to weeks.
 - e. With a large **effusion**, the electrocardiogram (ECG) may show **electrical alternans or low voltage**.
2. A chest radiograph may reveal **cardiomegaly** and may yield important information in support of tuberculous or neoplastic processes.
 3. Blood cultures along with sputum and gastric aspirate for tuberculosis should be done where such a diagnosis of purulent or tuberculous pericarditis is suspected (including in immunosuppressed immigrants). Pericardial or pleural biopsy may be necessary to diagnose tuberculosis.
 4. Blood tests may reveal leukocytosis or an elevated erythrocyte sedimentation rate, which are nonspecific markers of inflammation. Mild **elevations in the creatine kinase myocardial band (CK-MB) fraction or cardiac troponin levels can be seen** and suggest a more extensive acute inflammatory process involving the epicardium; significant elevations in these markers should raise suspicion for more extensive myocardial involvement, referred to as **myopericarditis**.
 5. **Echocardiography**
 - a. Pericarditis is not an echocardiographic diagnosis and a normal echocardiogram does not preclude pericarditis. Echocardiography should be performed when **symptoms last longer than a week, to evaluate for hemodynamic abnormalities**.
 - b. If the patient has had **recent cardiac surgery**, is **elderly**, or if there is a **suspicion for pericardial effusion**, **echocardiography** should be done as **part of the initial workup**.
 6. Computed tomography (CT), magnetic resonance imaging (MRI), or transesophageal echocardiography (TEE) can be done in select cases for further investigation of the pericardium (refer to Chapters 52, 51, and 68, respectively, for detailed discussions on these modalities).

D. Differential diagnosis

1. Chest pain from acute pericarditis can mimic **aortic dissection, pulmonary embolism, pneumothorax, or acute coronary syndrome**.
 2. Electrocardiographic changes can also mimic **myocardial ischemia**; however, the ST segments of pericarditis are usually concave upward with upright T waves. Echocardiography may assist in distinguishing between pericarditis and ischemia by assessing for segmental wall motion abnormalities, which are usually absent in pericarditis.
- E. **Therapy**. Most cases of acute pericarditis are **uncomplicated and self-limited and such patients can be managed in the outpatient setting**. However, **inpatient management should be considered in patients with large pericardial effusion or coexisting myocarditis**. These typically respond to conservative medical therapy. First-line therapy usually consists of **nonsteroidal anti-inflammatory drugs (NSAIDs) with the addition of colchicine in some cases**.

1. Medical therapy

- a. **Ibuprofen** has a good safety profile and is a reasonable first-line therapy at doses of 600 to 800 mg orally three times a day for at least 2 weeks. **Aspirin** 650 mg orally every 6 to 8 hours for 2 to 4 weeks is an alternative therapy. Other NSAID agents, including naproxen, seem to be similarly efficacious.
- b. If the **patient does not respond to NSAIDs**, or in cases of recurrent pericarditis, **colchicine** should be considered in addition to NSAIDs. A randomized controlled trial, colchicine for acute pericarditis (COPE), of 120 patients

with a first episode of acute pericarditis demonstrated superior efficacy of a combined regimen of aspirin with colchicine. The usual dosing of colchicine is 1 to 2 mg for the first day and then 0.5 to 1 mg daily for 3 months.

- c. **Prednisone** should be used only in patients with recurrent pericarditis with persistent symptoms despite NSAIDs and colchicine therapy or in cases where there is an underlying inflammatory disease that is responsive to corticosteroid therapy. Prednisone should be dosed at 1 to 1.5 mg/kg for at least 1 month and should be tapered slowly. In the COPE trial, **corticosteroid therapy was an independent risk factor for recurrence**.
 - d. **Post-MI pericarditis patients should *not* be treated with prednisone**, given the risk of myocardial rupture. Treatment with aspirin is recommended (650 mg every 6 hours).
 - e. In cases of suspected **purulent pericarditis, empiric antibiotic therapy directed against staphylococci and streptococci** should be instituted while cultures are pending.
 - f. For **tuberculous pericarditis**, standard triple drug therapy is recommended for at least 9 months, with 6 months of treatment following culture conversion.
 - g. Pericarditis due to Dressler's syndrome should be managed with NSAIDs or aspirin. If the condition is recurrent, a trial of prednisone may be warranted.
 - h. Intensive dialysis is the treatment of choice for symptomatic uremic pericarditis. **Dialysis is not necessary for patients who are asymptomatic** with relatively small pericardial effusions.
2. **Percutaneous therapy**
 - a. Because most cases of pericarditis are self-limited, there is no role for routine pericardiocentesis, intrapericardial administration of steroids, or pericardial biopsy.
 - b. In cases complicated by tamponade or suspected purulent effusion or neoplasm, pericardiocentesis should be performed. Pericardiocentesis should be reserved for large, hemodynamically compromising pericardial effusions or when fluid is needed for diagnostic purposes.
 - c. If the etiology is uncertain, **pericardial fluid should be sent for a hematocrit and a white blood cell count with differential, glucose, protein, cytologic, and microbiologic analyses (e.g., culture for various organisms and AFB staining)**. If there is a clinical suspicion of purulent pericarditis, pericardiocentesis should be performed promptly and the fluid sent for culture. If the pericardial fluid is **serosanguineous or grossly bloody**, the clinician should send it for cytologic examination, culture, and AFB staining.
 3. **Surgical therapy**
 - a. Subxiphoid pericardiostomy is usually performed for neoplastic pericarditis with rapidly recurrent pericardial effusions. Sclerotherapy with tetracycline has been performed in severe cases of neoplastic pericarditis; however, the procedure is painful and is associated with arrhythmias and risk for constrictive pericarditis.
 - b. Pericardiectomy is reserved for severe recurrent pericarditis. More commonly it is employed in the management of constrictive pericarditis, as discussed later in this chapter.
- F. **Follow-up**
 1. Most patients with idiopathic or viral pericarditis **should receive 1-month follow-up** to ensure that their symptoms have resolved and that no evidence of constrictive pericarditis exists.
 2. Patients with pericardial effusions should have serial echocardiograms to assess for recurrence or an increase in the size of the effusion.
 - G. **Prevention of postpericardiotomy syndrome (PPS)**. In a recent multicenter, double-blind, randomized trial, colchicine was found to be useful in preventing PPS and its related complication; however, this approach has not been widely used because of the relatively low incidence of clinically significant PPS.

H. Complications

1. **Recurrent pericarditis** can occur after an episode of acute idiopathic pericarditis, open heart surgery, cardiac trauma, or Dressler's syndrome. Natural history studies suggest that **recurrent pericarditis occurs in 20% to 30% of patients**. Recurrent pericarditis may be very bothersome. However, with appropriate management of exacerbations and prophylaxis, it frequently responds favorably and eventually peters out.
 - a. Clinical presentation is similar to that of acute pericarditis, with **variable onset** from months to years after the initial episode.
 - b. **Therapy.** NSAIDs and colchicine should be administered. **Only if patients fail to respond should prednisone be administered** (1 to 1.5 mg/kg) for at least 1 month and tapered slowly. Intravenous methylprednisolone can be given depending on the severity of symptoms. Most patients respond within a few days but may have recurrence with cessation of steroids. **Surgical pericardiectomy is reserved for patients with persistent recurrent pericarditis accompanied by severe chest pain despite aggressive medical therapy. It too may fail, as it is difficult to remove all of the pericardium surgically.**
 - c. **Prevention.** The COPE trial has shown that **colchicine is safe and effective in the prevention of recurrent pericarditis**.
2. Cardiac tamponade will occur in about 15% of patients, most commonly after a cardiac surgical intervention or with neoplasm.
3. **Constrictive pericarditis.** Approximately 9% of patients develop mild constrictive physiology. However, this usually resolves after 3 months. Some patients develop a subacute picture of **effusive–constrictive disease**, with both effusion and pericardial thickening. This may progress to symptomatic pericardial constriction. When it does so, the interval of onset of severe constrictive findings is much more rapid than in constriction without effusive changes.

III. CONSTRICTIVE PERICARDITIS results from **a fibrous thickening of the pericardium** secondary to chronic inflammation from a variety of injuries. Essentially, the **heart is encased by the rigid pericardium**, leading to a decrease in diastolic filling, an increase in intracardiac pressures, and a **dissociation of intracardiac pressure from intrathoracic pressure**. The hallmark of pericardial constriction is the **equalization of end-diastolic pressures in all four cardiac chambers**. The elevated cardiac pressures and diminished diastolic filling lead to increased venous pressure, both pulmonary and systemic, and thus to progressive **signs and symptoms of right and left heart failure**. Although constrictive pericarditis is a relatively uncommon cause of heart failure, recognition of this entity is important, as its **prevalence appears to be increasing and the diagnosis is often missed**.

- A. Causes of constrictive pericarditis.** The **factors involved in the development of constrictive pericarditis are varied** and are similar to those of acute pericarditis (Table 40.3). However, there is **a common pathophysiologic pathway** leading to **chronic inflammation and pericardial fibrosis**. Neoplastic disease is an exception because tumor infiltration of the pericardium is often responsible for constriction. The causes of constrictive pericarditis in the decreasing order of frequency are idiopathic factors, radiation therapy, postsurgical therapy, and infectious disease. This represents a significant change from a century ago when infectious disease, specifically tuberculosis, predominated.
1. Since the advent of effective antitubercular medications, the **number of cases attributable to tuberculosis has dropped precipitously in the United States**. However, tuberculosis remains the primary cause of constrictive pericarditis in most developing regions of the world.
 2. Similarly, **bacterial infections of the chest** continue to represent a large number of cases on a global scale, but these **have largely disappeared in the United States** following the introduction of antibiotics and improved drainage procedures.
 3. Most **“idiopathic”** cases are **likely infectious in nature**, due to viral infections caused by viruses such as **coxsackievirus and echovirus**; however, a clear etiologic

TABLE 40.3 Common Causes of Constrictive Pericarditis

Idiopathic
Infectious diseases
Tuberculosis
Bacterial
Viral (e.g., coxsackievirus B and echovirus)
Fungal
Parasitic
Trauma (including cardiac surgery)
Radiation
Inflammatory/immunologic disorder
Rheumatoid arthritis
Systemic lupus erythematosus
Scleroderma
Sarcoidosis
Neoplastic disease
Breast cancer
Lung cancer
Lymphoma
Mesothelioma
Melanoma
End-stage renal disease

link is rarely established. Less common infectious agents include fungal and parasitic organisms.

4. Constrictive pericarditis is a **late complication of radiation therapy**, generally occurring **many years after the administration of radiation**. Risk factors for development of constrictive pericarditis include duration of therapy, total amount of radiation administered, and volume of the heart in the radiation field. In contrast to other causes of constrictive pericarditis, where the myocardium is typically normal in structure and function, there may be **associated radiation damage to the myocardium**.
 5. Constrictive pericarditis is a well-documented **late complication of cardiac surgery, including** coronary artery bypass grafting and valvular surgery. **Risk factors** for development of postoperative constrictive pericarditis include **intraoperative hemorrhage into the pericardium, postoperative pericarditis**, and the occurrence of **postpericardiotomy syndrome**.
 6. End-stage renal disease, neoplastic disease (primarily breast, lung, and lymphoma), and connective tissue disease are less common causes that must be considered in the initial differential.
- B. Pathophysiology.** In constrictive pericarditis, there is **thickening and fibrosis of the pericardium with associated perimyocardial tethering**, often with superimposed calcification, resulting in **decreased ventricular compliance** (ventricular compliance = end-diastolic volume/end-diastolic pressure). However, in a small percentage of patients with constrictive pericarditis, the pericardium may not appear thickened on noninvasive imaging.

As the pericardium thickens and limits ventricular compliance, there is an **increased end-diastolic pressure for any given end-diastolic volume**. This increase in pressure **affects both ventricles equally** and effectively decreases diastolic filling and thus end-diastolic volume of both ventricles. The increased pressure is transmitted backward and results in elevated pulmonary venous and systemic venous pressures. **Equalization of end-diastolic pressures in all four cardiac chambers then ensues and is an important characteristic of constrictive pericarditis.**

1. The myocardium is generally normal in structure and function; therefore, **systole is unimpaired**.
2. Diastolic function, on the other hand, **is markedly altered** by the constrictive process. In early diastole, the ventricles expand normally, and there is rapid filling secondary to the elevated pulmonary and systemic pressures. Once the **ventricles reach the confines of the rigid pericardium**, there is an **immediate increase in ventricular pressure** and **diastolic filling comes to an abrupt halt**.
3. The result is that **nearly all ventricular filling occurs in the second phase of diastole (early filling)** with little contribution from the third phase (diastasis) and the fourth phase (atrial systole).

C. Physical signs and symptoms

1. The **early symptoms** of constrictive pericarditis are often insidious, and the patient may have nonspecific complaints such as **malaise, fatigue, and decreased exercise tolerance**.
2. As the disease progresses, **symptoms consistent with systemic congestion and low cardiac output**, such as **marked jugular venous distention, ascites, peripheral edema, and worsening exercise tolerance**, may predominate. Symptoms due to right-sided failure usually predominate over left-sided failure due to equalization of pressures.
3. **Examination of jugular veins.** Nearly all patients have **jugular venous distention**, which simply reflects the elevated right-sided pressures. Many patients demonstrate a lack of inspiratory fall in venous distention, known as **Kussmaul's sign**. This finding is sensitive but lacks specificity, as other conditions such as right ventricular (RV) hypertrophy and RV infarction also produce this sign. Observation of the jugular venous pulsations reveals a **prominent y descent that is produced by the rapid ventricular filling in early diastole**. The jugular venous pressure is sometimes so high in constrictive physiology that the level is not evident in the neck on examination with the patient at a 45° angle, and the diagnosis is, therefore, missed. **Appreciation of the height of the pressure may only be evident on examining the patient upright.**
4. **Cardiac examination.** Cardiac auscultation may reveal **muffled heart sounds** due to decreased transmission through the thickened pericardium. Because the mitral and tricuspid valves are nearly closed by the end of diastole, there may be a **soft first heart sound (S_1)**. **Occasionally, one may hear a pericardial knock** in early diastole (60 to 120 milliseconds after the second heart sound [S_2]). This represents the abrupt cessation of diastolic filling that occurs when further ventricular relaxation is impeded by the rigid pericardium. The pericardial knock **must be differentiated from other early diastolic sounds** such as an opening snap, third heart sound (S_3), and tumor plop. In general, the **pericardial knock is of a higher frequency, is heard best with the stethoscope diaphragm, and occurs slightly earlier than an S_3** . An opening snap may be similar in frequency and timing but is nearly always followed by a diastolic rumble.
5. **Pulmonary examination.** Auscultation of the lung fields may reveal **decreased breath sounds at the bases**, attributed to pleural effusions.
6. **Abdominal examination.** The abdominal examination may reveal evidence of right-sided heart failure, with **hepatomegaly and splenomegaly** being frequently noted. In **severe cases, there may be** liver dysfunction and **ascites**.

7. **Examination of the extremities.** Elevated central venous pressures due to RV impairment and sodium retention due to left ventricular (LV) impairment contribute to the development of **peripheral edema**.
- D. **Diagnostic testing.** Confirming the diagnosis of constrictive pericarditis often presents a challenge, since no gold standard test exists. **The clinician must rely on a collection of findings from multiple diagnostic modalities to detect both anatomic and pathophysiologic abnormalities.** Perhaps, the greatest challenge lies in differentiating constrictive pericarditis from restrictive cardiomyopathy.
 1. **Electrocardiography.** Low voltage is frequently seen with **generalized flattening of the T waves**. There may be **left atrial enlargement**. **Atrial fibrillation** is a common finding.
 2. **Chest radiograph.** Pericardial calcification is relatively common in advanced disease. The calcification is usually best appreciated with a lateral film and frequently involves the right ventricle and atrioventricular groove. **Pleural effusions** occur frequently, and there may be evidence of both **left and right atrial enlargement**.
 3. **Two-dimensional echocardiography**
 - a. **Septal bounce.** This is the **sudden cessation of septal motion**, as the heart abruptly stops filling upon meeting the rigid pericardium.
 - b. **Ventricular interdependence.** This is due to the fixed space in which cardiac filling occurs. Preferential filling of the right ventricle on inspiration causes the septum to move to the left, whereas on expiration the augmentation of LV filling causes the septum to move to the right.
 - c. **Inferior vena cava (IVC) plethora.** IVC is typically dilated and does not collapse, due to elevated right-sided pressures.
 4. **Doppler echocardiography.** Although imaging findings may suggest pericardial constriction, most of the findings described previously are relatively low in sensitivity and specificity. Doppler assessment of diastolic flow patterns and the respiratory changes in these patterns may provide **significant evidence for the presence of constrictive physiology** and assist in helping **exclude competing diagnoses**, such as restrictive cardiomyopathy.
 - a. **Respiratory variation in mitral and tricuspid flows.** In constrictive pericarditis, the thickened pericardium isolates the cardiac chambers from respiratory changes in intrathoracic pressures.
 - (1) During **inspiration**, the drop in intrathoracic pressure is transmitted to the pulmonary veins, but not to the left ventricle. This reduces the pressure gradient required for diastolic filling of the left ventricle; therefore, **a decrease in mitral flow is observed during inspiration**. Conversely, there is an **increased tricuspid flow during inspiration**. **Findings suggestive of constrictive physiology include the following:**
 - (a) **Mitral valve inflow.** Peak E velocity decreases by 33% or greater (Fig. 40.2).
 - (b) **Tricuspid valve inflow.** Peak E velocity increases by 44% or greater and peak A velocity increases by 38% or greater (Fig. 40.3).
 - (2) **Opposite changes are seen with expiration.** Increased intrathoracic pressure is transmitted to the pulmonary veins and this increases the driving pressure for LV filling. There is a **decreased tricuspid flow**. **The wide respiratory variation in peak E velocities helps to differentiate constrictive pericarditis from restrictive cardiomyopathy, in which minimal respiratory variation occurs** (Figs. 40.2 and 40.3).
 - b. **Pulmonary venous flow.** In a healthy individual, pulmonary venous flow consists of a peak velocity during ventricular systole (S wave) and a smaller peak velocity during ventricular diastole (D wave). There is normally little respiratory variation in these velocities. In constrictive pericarditis, there is an increase in early diastolic flow manifested as a larger D wave; therefore, the **pulmonary systolic/diastolic (S/D) flow ratio is decreased**. In addition, **both systolic**

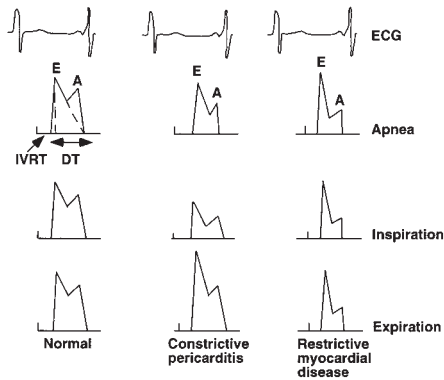


FIGURE 40.2 Respiratory variation in flow across the mitral valve in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. The peak early diastolic filling velocity is denoted as E and the peak late diastolic filling velocity (from atrial contraction) is denoted as A. The isovolumic relaxation time (IVRT) is the period between aortic valve closure and mitral valve opening. The deceleration time (DT) is the time it takes to go from peak E velocity to cessation of flow. In constrictive pericarditis, expiration results in a decreased IVRT and a marked increase in peak E and peak A velocities across the mitral valve. Similar changes are not observed in normals and those with restrictive disease. Patients with restriction have an increased E/A and shortened DT; however, there is no significant respiratory variation. ECG, electrocardiogram. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol.* 1993;22:1935–1943.

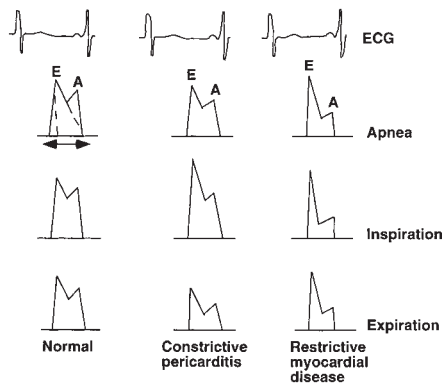


FIGURE 40.3 Respiratory variation in flow across the tricuspid valve in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. Constrictive pericarditis results in changes in flow across the tricuspid valve that are opposite to those described for the mitral valve in Figure 40.2. In constrictive pericarditis, inspiration results in increased peak E and peak A velocities across the tricuspid valve. Similar changes are not observed in normals and those with restrictive cardiomyopathy. Patients with restriction have an increased E/A and shortened DT; however, there is no significant respiratory variation. ECG, electrocardiogram. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transesophageal echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol.* 1993;22:1935–1943.

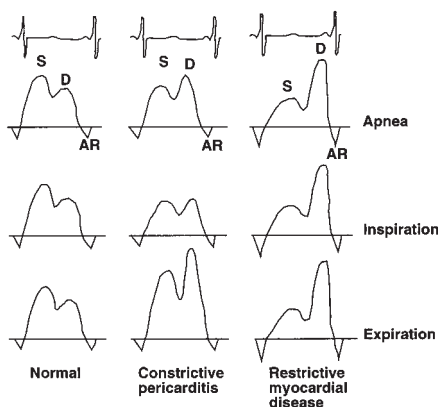


FIGURE 40.4 Respiratory variation in pulmonary venous flow in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. The peak pulmonary venous velocities during systole are denoted as the S wave and peak diastolic velocities are denoted as the D wave. The AR wave represents the small reversal in flow that is noted with atrial contraction. In constrictive pericarditis, there is a slight decrease in the S/D ratio and a marked increase in both velocities during expiration as compared with inspiration. This respiratory variation in pulmonary venous flows is not observed in normal individuals or those with restrictive disease. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transthoracic echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol.* 1993;22:1935–1943.

and diastolic pulmonary venous flows are markedly increased during **expiration**. This increase in expiratory pulmonary venous flow assists in distinguishing constrictive pericarditis from restrictive cardiomyopathy (Fig. 40.4).

- c. **Respiratory variation in hepatic vein flow.** Hepatic venous flow reflects right-sided filling in much the same manner that pulmonary venous flow reflects left-sided filling. It is represented similarly by an S wave and a D wave, as well as a reversal in flow in atrial systole (AR wave) and a reversal in flow due to late ventricular systole (VR wave). Individuals with constrictive pericarditis and those without have a more prominent systolic flow than a diastolic flow; however, individuals without constrictive pericarditis have little respiratory variation in these flow velocities. **In constrictive pericarditis, there is a marked increase in the D wave during inspiration and a significant blunting during expiration. Expiration also results in prominent diastolic flow reversal demonstrated by increase in AR and VR.** In restrictive disease there is a reversal in systolic-to-diastolic flow ratios, but no respiratory variation exists in these flow velocities (Fig. 40.5).

d. **Doppler tissue imaging**

(a) Myocardial relaxation, and thus annular velocity, is typically **reduced in restrictive cardiomyopathies**, but the Doppler velocities of the medial mitral valve annulus in early diastole are **normal or slightly increased** in constrictive pericarditis. The pattern of these velocities is altered in constrictive pericarditis (Fig. 40.6). In normal individuals, peak early diastolic annular tissue velocity (E') at the lateral mitral annulus is higher than that at the medial mitral annulus. **This relationship between the lateral and medial mitral annuli is reversed (“annulus reversus”) in constriction, where E' at the lateral mitral annulus is typically lower than E' at the medial mitral annulus.** This is attributed to tethering of the LV lateral free wall to the pericardium in constriction. Similar effects of perimycocardial tethering on the RV free wall have been reported. These patterns

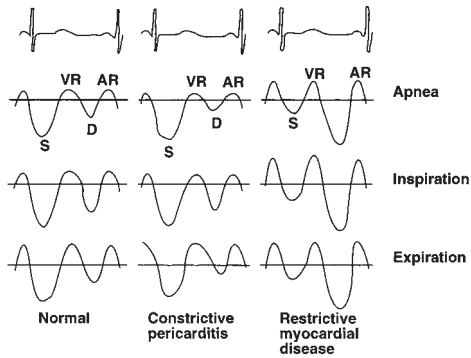


FIGURE 40.5 Respiratory variation in hepatic vein flow in normal circumstance, constrictive pericarditis, and restrictive cardiomyopathy. Similar to pulmonary vein flow, the S wave represents peak systolic flow velocity and the D wave represents peak diastolic flow velocity. VR denotes the reversal in flow noted in late systole, and AR is the reversal in flow due to atrial contraction. In both normal subjects and those with constrictive pericarditis, there is an increase in both S and D waves with inspiration. During expiration, there is little change in normal subjects; however, those with constrictive pericarditis will have a marked drop in both S and D waves and an increase in both VR and AR. Adapted from Klein AL, Cohen GI, Pietrolungo JF, et al. Differentiation of constrictive pericarditis from restrictive cardiomyopathy by Doppler transthoracic echocardiographic measurements of respiratory variations in pulmonary venous flows. *J Am Coll Cardiol.* 1993;22:1935–1943.

may not occur in all cases of constrictive pericarditis because of the heterogeneity of tethering (annular sparing constriction) and coexisting myocardial disease.

(b) In restrictive cardiomyopathies, the early diastolic annular velocity is characteristically **low at both medial and lateral mitral annuli** (< 8 cm/s).

5. **Cardiac catheterization.** The hemodynamics obtained in the catheterization laboratory assists in both diagnosing constrictive pericarditis and differentiating it from restrictive cardiomyopathy. In general, both right and left heart catheterization are performed to obtain simultaneous ventricular pressure readings.

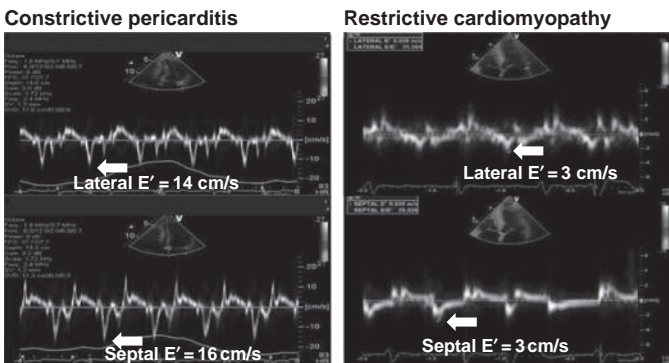


FIGURE 40.6 Annular tissue velocities from two patients. Note that tissue velocities are lower in restrictive cardiomyopathy compared with constrictive pericarditis. In addition, lateral E' is lower than septal E' in constrictive pericarditis, which is attributable to perimyocardial tethering of the lateral left ventricular free wall.

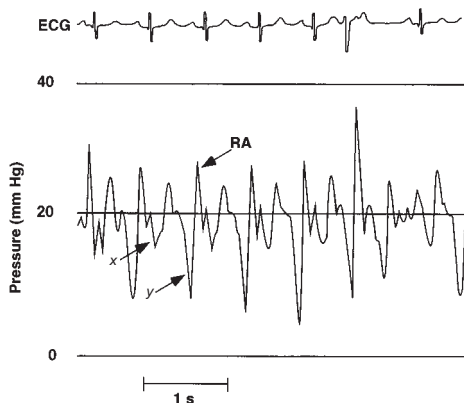


FIGURE 40.7 Right atrial (RA) pressure waveform in constrictive pericarditis. The preserved *x* descent and the prominent *y* descent contribute to the classic W-shaped atrial waveform. Adapted from Lorell BH, Grossman W. Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade in cardiac catheterization. In: Baim DS, Grossman W, eds. *Angiography and Intervention*. 5th ed. Baltimore, MD: Williams & Wilkins; 1996:801–822. ECG, electrocardiogram.

- a. **Atrial pressures.** The right atrial pressure waveform has been described as having a **W-shaped configuration**. This morphology is produced by a prominent *a* wave as the atria contract against an elevated ventricular pressure, an exaggerated *x* descent, and a steep *y* descent, due to rapid ventricular filling in early diastole (Fig. 40.7).
- b. **Ventricular pressures**
 - (1) Ventricular pressure waveforms demonstrate the classic **dip-and-plateau** physiology, commonly referred to as the **square root sign** (Fig. 40.8).

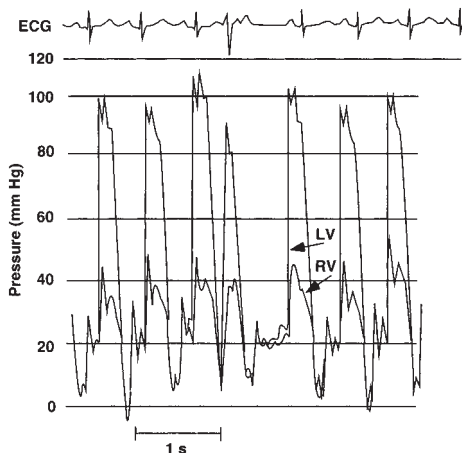


FIGURE 40.8 Right and left ventricular waveforms in constrictive pericarditis. Note the equalization of left ventricular and right ventricular end-diastolic pressures, generally within 5 mm Hg of one another. The rapid early diastolic filling and subsequent abrupt cessation of flow due to the rigid pericardium produces a dip-and-plateau waveform (square root sign), appreciated best in this waveform following the premature ventricular contraction. LV, left ventricular; RV, right ventricular; ECG, electrocardiogram. Adapted from Lorell BH, Grossman W. Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade in cardiac catheterization. In: Baim DS, Grossman W, eds. *Angiography and Intervention*. 5th ed. Baltimore, MD: Williams & Wilkins; 1996:801–822.

- (2) The initial downward deflection reflects the drop in pressure during the isovolumetric relaxation period. The subsequent upward deflection reflects early diastolic filling. The terminal plateau represents the cessation of flow that occurs once the limit of the rigid pericardium has been reached.
- (3) The end-diastolic pressures of both ventricles are not only elevated but also equal, with a < 5 mm Hg difference between the two. The RV systolic pressure is generally < 55 mm Hg, with an RV end-diastolic pressure that is one-third greater than the RV systolic pressure. **These findings assist in differentiating constrictive pericarditis from restrictive cardiomyopathy, where RV systolic pressure is often elevated to > 55 mm Hg.**
- (4) **Meticulously performed cardiac catheterization can demonstrate ventricular interdependence, which is a hallmark of constrictive pericarditis and is most useful in differentiating constrictive pericarditis from restrictive cardiomyopathy.** The ratio of the RV to LV systolic pressure–time area during inspiration versus expiration (systolic area index) has been shown to be a useful measure of enhanced interventricular interaction (Fig. 40.9).
- (5) **Hypovolemia can mask characteristic features of constrictive pericarditis, and fluid challenge in the cardiac catheterization laboratory may be required to unmask ventricular interdependence in patients who are volume depleted.**

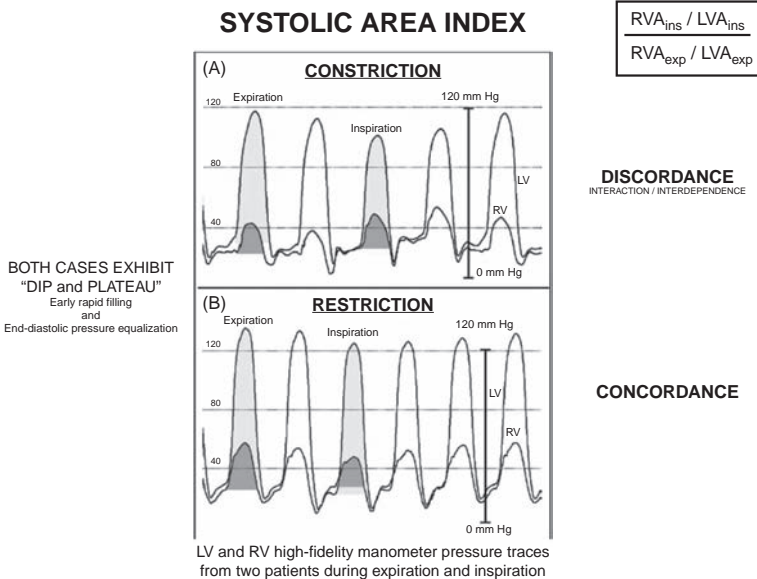


FIGURE 40.9 Respiratory ventricular interaction between RV and LV systolic area indexes in patients with constriction (A) and restriction (B). Note that in constrictive pericarditis patients (A), there is a rise in the area of RV pressure curve (darker-shaded area) and reduction in the area of LV pressure curve (lighter-shaded area), whereas in restrictive cardiomyopathy patients, there is a drop in the area of RV pressure curve during inspiration, with no change in the area of LV systolic pressure curve. LV, left ventricular; RV, right ventricular. RVA_{ins} , RV systolic area in inspirations; RVA_{exp} , RV systolic area in expirations; LVA_{ins} , LV systolic area in inspirations; LVA_{exp} , LV systolic area in expirations; Adapted from *J Am Coll Cardiol.* 2008;51:315-319.

(6) Role of cardiac CT and MRI in constrictive pericarditis

- (a) Cardiac CT** in constrictive pericarditis provides a superior three-dimensional delineation of the pericardium in comparison with echocardiography. A thickened pericardium > 4 mm is supportive of the diagnosis, although normal pericardial thickness does not exclude constrictive pericarditis. In a series reported by Talreja et al., (1) 18% of constrictive pericarditis patients had normal pericardial thickness. Cardiac CT is the best modality for assessing pericardial calcification, which may assist in surgical planning.
- (b) Cardiac magnetic resonance imaging (CMR)** provides both anatomical and hemodynamic information in constrictive pericarditis, without the radiation exposure that is associated with cardiac CT. Like echocardiography, MRI may demonstrate features of ventricular interdependence such as septal bounce and respirophasic variation in septal excursion. In addition, MRI is the best modality to assess pericardial inflammation, where an initial trial of medical therapy may be considered. Furthermore, MRI is excellent at tissue characterization, quantifying LV and RV systolic function, which is of value in patients where there is diagnostic uncertainty and restrictive myocardial disease is a consideration. CMR should be the non-invasive imaging modality of choice in a patient who is suspected to have constrictive pericarditis but has a nondiagnostic echo. The main limitation of MRI is that it cannot be performed in patients with MRI-incompatible implants or devices. MRI is also inferior to cardiac CT in assessing pericardial calcification.

(7) Differentiating constriction from restriction

In clinical practice, it is often challenging to differentiate constrictive pericarditis from restrictive cardiomyopathy, as both present as heart failure with preserved ejection fraction. Poor LV filling in constrictive pericarditis results from external constraints of a rigid pericardium, whereas a small LV cavity with impaired LV relaxation is usually the cause of diastolic dysfunction in restrictive cardiomyopathy. It is critical to differentiate between the two because of the different treatment strategies. Constrictive pericarditis is a potentially curable disease, whereas treatment options in restrictive cardiomyopathy are often limited to medical therapy. Despite the hemodynamic similarities, there are several key findings by echocardiography, cardiac catheterization, and CMR that can be used to differentiate these two clinical entities and are described in Table 40.4.

(8) Practical approach to diagnosing constrictive pericarditis

Basic workup of a patient with clinical features of constrictive pericarditis includes ECG and chest x-ray, which may reveal calcification. This should be followed by comprehensive echocardiography with a respirometer. If there is evidence of calcification on x-ray and echocardiography and there are convincing features of calcific constrictive pericarditis, then the patient may be directly referred to a cardiac surgeon. Some surgeons desire a pre-operative right heart catheterization not only to confirm the diagnosis but also to get an accurate assessment of the cardiac index, which may assist in surgical planning. CMR should be strongly considered in cases where the echocardiogram is nondiagnostic and in patients where transient constriction is suspected. CMR will not only confirm the diagnoses of constrictive pericarditis but also assess pericardial inflammation. There is emerging evidence supporting medical therapy with anti-inflammatory medication as an initial strategy in a patient with inflamed constrictive pericarditis or effusive-constrictive disease. Cardiac CT should be limited to patients who

TABLE 40.4 Key Findings Used to Differentiate Constriction from Restriction

Investigation	Constrictive pericarditis	Restrictive cardiomyopathy
Echocardiography		
Annular tissue velocity (E')	Preserved except at lateral mitral annulus and right lateral tricuspid annulus	Reduced
Diastolic dysfunction	Present	Present
Respirophasic interventricular septal shift	Present	Absent
Respirophasic variation in transvalvular/hepatic vein flow	Present	Absent
LV wall thickness	Normal	Normal or increased
Perimyocardial slippage (motion of LV, RV, and atrial free wall)	Reduced	Normal or reduced
Cardiac catheterization		
Elevated LVEDP	Present (equalization of diastolic pressures in all four chambers that are more suggestive of constriction)	Present
LV/RV discordance	Present	Absent
Cardiac MRI		
Respirophasic shift of interventricular septum	Present	Absent
Pericardial thickening or enhancement	Normal or increased	Normal
Myocardial scarring detected by post-gadolinium enhancement	Absent unless coexisting cardiomyopathy	Present

LV, left ventricular; RV, right ventricular; LVEDP, left ventricular end-diastolic pressure; MRI, magnetic resonance imaging.

are unable to undergo CMR or cases where three-dimensional assessments of pericardial calcification are warranted for surgical planning.

E. Therapy. Pericardiectomy is preferred in most cases, although there are certain patient populations in which medical therapy is appropriate.

1. Medical therapy

- Patients who have NYHA class I symptoms may initially be treated with diuretics and a low sodium diet. One case series of 36 patients demonstrated resolution of pericardial constriction with the use of NSAIDs, colchicine, and/or steroids. However, most of these patients ultimately require pericardiectomy.
- Medical therapy is also appropriate in **patients with severe comorbid illnesses** that limit life expectancy and/or place them at an unacceptably high risk for operative mortality. In addition trial of medical therapy maybe appropriate in inflammatory constrictive pericarditis.

2. Surgical therapy

- a. The treatment of choice is pericardiectomy. More than 90% of patients will report symptomatic improvement following the procedure.
- b. However, pericardiectomy carries an **operative mortality** that is reported to range from **5% to 20%**. The etiology of constrictive pericarditis can predict perioperative mortality. Patients who have constriction due to viral or idiopathic pericarditis have better outcomes than those who have radiation-induced constriction. Those patients with a poor preoperative functional class are at highest risk for perioperative death; therefore, most physicians advocate **early surgical intervention**.

IV. PERICARDIAL EFFUSION is a common clinical entity that is routinely diagnosed using echocardiography. It may be asymptomatic or present as life-threatening tamponade. **The presenting syndrome depends on the volume, the rate of accumulation, and the characteristics of the fluid.** Large effusions may be found unexpectedly and be asymptomatic, whereas rapidly accumulating small effusions may result in tamponade. An unstretched pericardium accommodates only 80 to 200 mL of rapidly accumulating fluid, without a significant change in hemodynamics. In contrast, the pericardial space may accumulate up to 2 L of fluid without any hemodynamic or clinical sequelae if this occurs slowly. **Compressive physiology** may occur with rapid accumulation of smaller amounts of fluid if the pericardium is stiff from fibrosis or infiltration by a tumor.

A. Clinical presentation

1. Slowly developing pericardial effusions, with no elevation of intrapericardial pressures, are **usually asymptomatic**.
2. Patients may complain of a **constant dull ache or pressure in the chest**.
3. There may also be a variety of symptoms from the space-occupying effects of the pericardial fluid on other organs in the chest. These include **dysphagia** from esophageal compression, **dyspnea** from lung compression and atelectasis, **hiccups** from compression of the phrenic nerve, and **nausea and abdominal fullness** from pressure on adjacent abdominal organs.
4. Large volume effusions may be associated with muffled heart sounds, Ewart's sign (dullness to percussion, bronchial breath sounds, and egophony below the angle of the left scapula), and rales in the lung field secondary to compression.
5. **Sinus tachycardia and hypotension are signs of hemodynamic compromise.**
6. **Patients with tamponade will have a pulsus paradoxus > 10 mm Hg.** The total intrapericardial volume is fixed; therefore, during inspiration, filling of the right ventricle pushes the septum into the left ventricle. This impairs left-sided filling, and there is a drop in systolic pressure during inspiration. Pulsus paradoxus is **not specific to cardiac tamponade** but may be seen in severe obstructive pulmonary disease, RV infarction, pulmonary embolism, or asthma.
7. Patients with tamponade will have jugular venous distention, and the x descent is typically the predominant waveform. **Beck's triad** includes jugular venous distention, distant heart sounds, and hypotension.

B. Etiology. Any cause of acute or chronic pericarditis (Table 40.5) may lead to the development of a pericardial effusion. Common causes of large chronic effusions include idiopathic pericarditis, uremia, pericarditis from malignancy or myxedema, congestive heart failure, nephrotic syndrome, cirrhosis, hypothyroidism, postcardiac surgery, and certain medications.

C. Laboratory examination and diagnostic testing

1. **Electrocardiogram.** The classic electrocardiographic finding consists of a **low-voltage tracing**. **Electrical alternans** is a marker of a massive pericardial effusion.
2. Chest radiography. **Increase in cardiothoracic ratio may occur if > 250 mL of fluid has accumulated.** **Increase in cardiothoracic ratio** with a large prominent superior vena cava, azygous vein, and decreased pulmonary vascularity should suggest the diagnosis of pericardial effusion.

TABLE 40.5 Causes of Pericardial Effusion

Idiopathic	Tuberculosis
Acute myocardial infarction	<i>Salmonella</i>
Delayed postmyocardial–pericardial injury syndromes	Psittacosis
Postmyocardial infarction syndrome (Dressler's syndrome)	Tularemia
Postpericardiotomy syndrome	Bacterial endocarditis
Metabolic	Fungal infections
Uremia	Histoplasmosis
Myxedema	Aspergillosis
Hypoalbuminemia	Blastomycosis
Radiation	Coccidioidomycosis
Dissecting thoracic aneurysm	Fungal endocarditis
Trauma	Other infections
Pericardiotomy	Amebiasis
Indirect trauma to the chest	<i>Echinococcus</i>
Percutaneous cardiac interventions	Lyme disease
Perforation of the heart by indwelling catheters	Mycoplasma pneumonia
	Rickettsia
Viral infections	Tumors
Coxsackieviruses A, B5, and B6	Primary
Echovirus	Mesothelioma
Adenovirus	Teratoma
Mumps virus	Fibroma
Hepatitis B virus	Leiomyofibroma and sarcoma
Infectious mononucleosis	Lipoma and angioma
Influenza	Metastatic
<i>Lymphogranuloma venereum</i>	Breast carcinoma
Varicella	Bronchogenic carcinoma
Human immunodeficiency virus	Lymphoma
Bacterial infections	Leukemia melanoma
<i>Staphylococcus</i>	Others
<i>Streptococcus</i>	Immunologic/inflammatory disorders
<i>Pneumococcus</i>	Rheumatic fever
<i>Haemophilus influenzae</i>	Systemic lupus erythematosus
<i>Neisseria gonorrhoeae</i>	Ankylosing spondylitis
<i>Neisseria meningitidis</i>	Rheumatoid arthritis
<i>Legionella pneumophila</i>	Vasculitis
	Wegener's granulomatosis

(Continued)

TABLE 40.5 Causes of Pericardial Effusion (*Continued*)

Polyarteritis nodosa	Hydralazine
Scleroderma	Heparin
Dermatomyositis	Warfarin
Sarcoidosis	Phenytoin
Inflammatory bowel disease	Phenylbutazone
Whipple's disease	Cromolyn sodium
Behçet's syndrome	Dantrolene
Reiter's syndrome	Methysergide
Temporal arteritis	Doxorubicin
Amyloidosis	Penicillin
Familial Mediterranean fever	Minoxidil
Drugs	Colony-stimulating factor
Procainamide	Interleukin-2

3. Transthoracic echocardiogram (TTE) is the **modality of choice** for diagnosing and following pericardial effusions. It allows for accurate diagnosis, ensures the adequacy of drainage procedures, and enables a qualitative assessment in following pericardial effusions. Echocardiography is **not** useful in differentiating among the different etiologic factors.

- a. Two-dimensional echocardiographic findings are as follows:

- (1) An **echo-free space** is found between the visceral and parietal pericardium in both systole and diastole.
- (2) The **motion of the parietal pericardium is decreased**.
- (3) When the effusion is large, the **entire heart swings in the pericardium**. This swinging or rocking may occur along both the anteroposterior and the mediolateral axes of the heart, and it is thought to be the mechanism for electrical alternans seen on the ECG.

- b. The Doppler echo findings in cardiac tamponade are described subsequently.

- (1) Small effusions (< 100 mL) tend to localize at the posterior wall distal to the atrioventricular ring. These tend to be < 1 cm in width.
- (2) Moderate effusions (100 to 500 mL). A moderate effusion could also be classified as one that surrounds the heart **but is 1 cm or less at its greatest width**.
- (3) Large effusions (> 500 mL). Here, although the posterior accumulation continues, the heart seems to settle posteriorly with a greater expansion of the pericardial space laterally, apically, and anteriorly. The **effusion is > 1 cm at its widest point**.

- c. The following may mimic a pericardial effusion on two-dimensional echocardiography.

- (1) Pericardial fat tends to be **localized anteriorly**. Unless loculated, a pericardial effusion localized to the anterior wall is very rare.
- (2) Seventy percent of **pericardial cysts** are found adjacent to the right cardiophrenic junction and adjacent to but separate from the right atrium in the apical four-chamber view.

- (3) A pleural effusion can be differentiated from a pericardial effusion by virtue of the **position of the descending thoracic aorta in the parasternal long-axis view**. If the fluid is based in the pericardium, the aorta is displaced posteriorly to the effusion, away from the posterior wall of the left atrium. If the fluid is pleural based, the aorta retains its position immediately below the left atrium. Lung parenchyma may be seen in the pleural fluid.
 - (4) Other mimics of pericardial effusions are pericardial fibrous bands and pericardial calcification, anterior mediastinal tumors, peritoneal fluid, and a giant left atrium.
4. **Magnetic resonance imaging.** Although not usually required, MRI offers high sensitivity in the detection of pericardial effusions. It outlines the distribution and provides an estimate of the pericardial fluid volume that correlates well with echocardiography. It is very effective in facilitating detection of loculated pericardial effusions and pericardial thickening. Because of its high tissue contrast, MRI allows the visualization of the pericardium in multiple planes. It can also differentiate simple from complex effusions and pericardial fat from pathologic thickening.
 5. **Computed tomography.** Using high-resolution axial images, CT provides excellent visualization of the pericardium. The size and distribution of the pericardial effusion are easily obtained using this technique. Moreover, differentiation among blood, exudate, chyle, and serous fluid may be achieved owing to the different attenuation coefficients for these substances.
 6. Diagnostic pericardiocentesis and pericardial fluid examination should be considered in patients with large effusions without clear etiology. Aspirated pericardial fluid should be carefully inspected and immediately placed in sterile tubes for biochemical, microbiologic, and cytologic examination.
- D. Therapy.** The management of pericardial effusions depends on the underlying etiologic factor, volume, and hemodynamic significance.
1. **Pericardiocentesis** (see Chapter 69). Although the cause of the effusion is important, it can often be determined without pericardiocentesis by virtue of the clinical, systemic, and laboratory features of the presenting condition.
 - a. Pericardiocentesis is **indicated if malignant, bacterial, mycobacterial, or fungal pericardial effusion is suspected**.
 - b. **Pericardiocentesis is an indication in the setting of large pericardial effusion with associated pericardial tamponade (see subsequent text)**.
 - c. With large effusions of recent onset, close clinical and echocardiographic follow-up is warranted. Pericardiocentesis **may be warranted in large asymptomatic pericardial effusions** when there are echocardiographic features of early tamponade.
 2. Anticoagulation is best avoided until the effusion has resolved.
- V. Cardiac tamponade** occurs when an increase in pericardial fluid raises intrapericardial pressure and impairs diastolic filling. Cardiac tamponade is characterized by **elevated intracardiac pressures, a progressive limitation of ventricular diastolic filling, and a reduction in cardiac output**.
- A. Pathophysiology**
1. There appears to be an **inverse relationship between the volume of the pericardial effusion and the cardiac output once a critical volume is reached**. Beyond this, small increments in pericardial volume result in large increases in intrapericardial pressure. This critical volume depends on the compliance of the pericardium, the rate of fluid accumulation, and the status of the pericardial lining (infiltrations, calcification, or fibrosis).
 2. The raised intrapericardial pressure results in a **decreased transmural distending pressure that results in decreased diastolic filling**.

3. The **cardiac output is initially maintained** by a heightened adrenergic tone, resulting in a resting tachycardia and peripheral vasoconstriction.
 4. In severe tamponade, the compensatory mechanisms fail, resulting in a decreased cardiac output. Reduced coronary perfusion may cause subendocardial hypoperfusion, further compromising the stroke volume and the cardiac output. The finite space around the heart chambers also results in the equalization of filling pressures with that in the pericardium.
 5. Following cardiac surgery, localized **pericardial hematoma** rather than fluid may impair filling of the heart. This most commonly occurs around the right atrium, is easily overlooked, and is difficult to diagnose using TTE. TEE should be considered in cases where **pericardial hematoma** is suspected but TTE images are nondiagnostic.
- B. Clinical presentation.** The signs and symptoms of cardiac tamponade all reflect a low cardiac output: **restlessness, agitation, drowsiness, or stupor; decreased urine output; dyspnea; chest discomfort and syncope or near syncope; and weakness, anorexia, and weight loss with a chronic effusion.**
1. **Physical findings**
 - (a) Raised central venous pressure. Characterized by a prominent *x* descent and an attenuated or absent *y* descent.
 - (b) Tachypnea. Reflects elevated pulmonary venous pressure.
 - (c) Tachycardia. Compensatory due to the low output state.
 - (d) Diminished heart sounds. Decreased transmission through the fluid-filled pericardium. A pericardial friction rub may be present in some cases.
 - (e) Pulsus paradoxus as described previously.
 - (f) **Hypotension (in severe cases).**
- C. Laboratory examination and diagnostic testing**
1. TTE should always be performed when the diagnosis of cardiac tamponade is suspected. An echocardiogram may suggest findings consistent with cardiac tamponade, but the clinical diagnosis requires **synthesis of both bedside and echocardiographic findings.**
 - a. Echocardiographic signs of cardiac tamponade include the following:
 - (1) **Pericardial effusion.**
 - (2) Right atrial diastolic collapse typically begins in late diastole and continues into ventricular systole. It is best seen in the parasternal short-axis view, the subcostal view, and the apical four-chamber view. It is a **very sensitive sign, but its specificity is 82%**, with a positive predictive value of 50%. **The longer the duration of diastolic collapse, the more specific it is for tamponade.**
 - (3) RV early diastolic collapse (or RV diastolic inversion). **Although very sensitive in medical patients, it is less so in surgical patients due to the loculated nature of these effusions and the presence of adhesions.** When present, the collapse is described as a persistent posterior or inward movement of the RV free wall in diastole. It is seen most commonly in the anterior RV free wall and infundibulum with patients in the supine position. The parasternal long-axis and short-axis views of the heart are the best for evaluating this sign; M-mode recording through the right ventricle helps to outline the timing and duration of the event. **Isolated RV diastolic collapse appears to occur before the onset of clinical tamponade.** Conditions that raise RV intracavity volume and RV pressure (pulmonary hypertension, RV hypertrophy, and RV infarction) delay the occurrence of RV diastolic collapse until higher intrapericardial pressures are reached.
 - (4) Left atrial diastolic collapse—a rare but specific sign of tamponade.
 - (5) Abnormal inspiratory increase of **RV dimensions** with abnormal inspiratory decrease of LV dimensions.
 - (6) Respiratory variation in atrioventricular valve flow pattern, with an abnormal inspiratory increase in tricuspid valve flow and abnormal

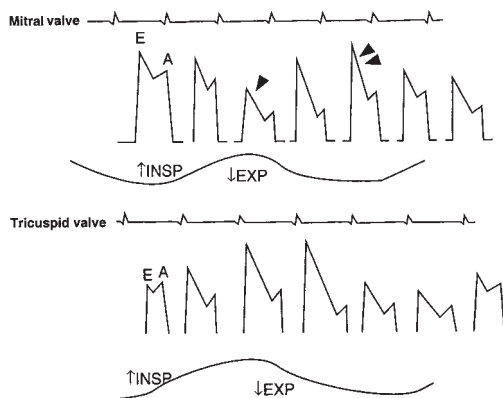


FIGURE 40.10 Pulsed wave Doppler for the mitral and tricuspid valves in a patient with cardiac tamponade. Note the marked respiratory variation of the inflow pattern, which in tamponade is a typical physiologic finding. INSP, inspiration; EXP, expiration.

inspiratory decrease in mitral valve flow (Fig. 40.10). Normally inspiration causes a decrease in mitral valve flow of up to 10% and an increase in tricuspid valve flow of up to 7%. **A decrease of the transmitral E wave of > 25% on inspiration is highly suggestive of significant tamponade.** A reduction of the tricuspid E wave of > 40%, together with prominent hepatic venous flow reversal during expiration, also suggests tamponade.

- (7) IVC plethora. Failure to decrease the proximal diameter by at least 50% on sniff or deep inspiration has 97% sensitivity but only 40% specificity for tamponade physiology.
2. TEE is indicated in the postoperative patient with clinical signs of tamponade and inadequate surface images or in whom fluid is not present in the pericardium. TEE is highly sensitive for detecting hematoma in this setting.
3. Right heart catheterization is not necessary in patients for whom clinical and echocardiographic findings are consistent with tamponade and, in fact, may produce a delay in definitive treatment. However, right heart catheterization may be helpful in certain “borderline” cases for confirmation of the diagnosis of tamponade, quantitation of the hemodynamic compromise, and continuous assessment following pericardiocentesis. This is especially the case if pericardiocentesis is technically challenging.
 - a. The **hemodynamic findings** include **equalization (within 4 mm Hg) of the right arterial pressure, pulmonary capillary wedge pressure (PCWP), pulmonary artery diastolic pressure, and RV middiastolic pressure**, which are raised usually between 10 and 30 mm Hg; the right arterial pressure reveals a **preserved x descent with an absent or attenuated y descent**; during expiration, the PCWP is slightly greater than the intrapericardial pressure that promotes filling of the left heart. With inspiration, the PCWP decreases (transiently), rendering a low or negative pressure gradient between the pulmonary venous circulation and the left heart.
 - b. Following pericardiocentesis, there is an initial decrease in all pressures (right atrial, RV diastolic, intrapericardial, PCWP, and LV end-diastolic). As the intrapericardial pressures continue to fall below the right atrial pressure, the y descent recovers to baseline. This may take as little as 50 mL of fluid

aspiration, due to the steep nature of the pressure–volume curve of the pericardium. These changes are accompanied by an increase in blood pressure and abolition of the pulsus paradoxus. Only with adequate hemodynamic monitoring, including arterial line and right heart catheterization, can these changes be followed. Lack of fall in atrial pressures post pericardiocentesis may indicate an effusive–constrictive process.

- c. **Effusive–constrictive pericarditis** (constrictive epicarditis). Effusive–constrictive pericarditis has been described in patients with pericardial tamponade in whom intracardiac pressures remain elevated despite the relief of intrapericardial pressure post pericardiocentesis. Effusive–constrictive pericarditis is unique, as there is predominant involvement of visceral pericardium (epicardium), called constrictive epicarditis by some authors. Some patients may have resolution with a conservative approach but others require extensive epicardiectomy, which should be performed at experienced centers as it is technically challenging.

D. Therapy

1. **Priority of therapy.** Once the diagnosis of tamponade is made, one needs to consider immediate **drainage**. The timing and method of drainage ultimately depend on the etiology of the effusion, the patient's level of acuity, and the availability of trained physicians. The options include needle pericardiocentesis and surgical drainage (subxiphoid pericardiectomy, pericardial window, and subtotal pericardiectomy).
2. **Medical therapy.** Optimal medical management is important and includes volume expansion, inotropic support if the patient is hypotensive, and avoidance of diuretics or vasodilators.
3. **Percutaneous therapy**
 - a. Pericardiocentesis allows the rapid drainage of pericardial fluid. Advantages are that it **can be performed quickly, is less invasive than other drainage methods, and requires minimal preparation**. Complications include laceration of the heart, coronary arteries, or lung. There is also the possibility of recurrent effusions or incomplete drainage. Pericardiocentesis is not recommended for small (< 1 cm) effusions or for those characterized by loculation, adhesions, or fibrinous stranding (see Chapter 69).
 - b. Percutaneous balloon pericardiomy is a technique involving balloon dilation of the pericardium after securing access to the pericardial space with a transcatheter approach. It has been used for large pericardial effusions, particularly when caused by malignancy.
4. **Surgical therapy.** Surgical drainage allows for a more complete drainage and is preferred if there is a high likelihood of recurrence. In addition, a surgical approach permits direct examination of the pericardium and access to the pericardial tissue for histopathologic and microbiologic diagnoses and has the capability to drain loculated effusions. Surgical drainage is associated with more pain, a longer recovery time, and more periprocedural morbidity.

ACKNOWLEDGMENTS: *The author thanks Drs. Debra Kwon, Jenny Wu, Stanley Chetcutti, and Joel Reginaldi for their contributions to earlier editions of this chapter.*

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Cardiac Tumors

- I. INTRODUCTION.** Cardiac neoplasms are **rare** in comparison with other forms of heart disease. Although secondary tumors of the heart are by definition malignant, primary tumors may be either benign or malignant. **Primary cardiac tumors occur approximately 30 times less frequently than cardiac metastases.** In most autopsy studies, the reported prevalence of primary tumors of the heart ranges from 0.001% to 0.03%, and about 75% are benign. Despite the relatively low prevalence, advances in curative operative therapy have made antemortem diagnosis of these tumors more clinically relevant.
- II. CLINICAL PRESENTATION.** Cardiac tumors often present with very nonspecific signs and symptoms. Patient complaints may be attributable to constitutional manifestations, embolic phenomena, or direct cardiac invasion/mass effect.
- A. Constitutional symptoms.** Many tumors, especially myxomas, are associated with a wide variety of systemic manifestations. Fever, chills, malaise, cachexia, and weight loss are not uncommon. Corresponding laboratory abnormalities, including leukocytosis, thrombocytosis or thrombocytopenia, hypergammaglobulinemia, as well as elevated erythrocyte sedimentation rate and C-reactive protein levels are frequently present as well. These findings are likely attributable to the constitutive production of **inflammatory cytokines** by the tumor or due to release from tumor necrosis. Myxoma cell production of **interleukin-6** and elevation of **antimyocardial antibodies** have been documented, with levels of these serum markers normalizing after tumor resection. Not surprisingly, patients with cardiac tumors often carry an incorrect antecedent diagnosis of collagen vascular disease, chronic infection, or noncardiac malignancy.
- B. Embolic phenomena.** Tumor embolization may account for the initial presenting symptoms, via either direct embolization of tumor fragments or thromboemboli released from the tumor surface. The type of emboli is dependent on tumor **location** as well as the presence of intracardiac shunts. **Right-sided** tumors, and left-sided tumors with left-to-right shunts, result in pulmonary emboli and if untreated may result in cor pulmonale. It may be difficult to clinically differentiate pulmonary tumor emboli from those due to venous thromboembolic disease. Chest radiography is usually not helpful. However, noninvasive imaging often has two unique characteristics that help differentiate tumor emboli from venous thromboemboli. First, tumor emboli may result in completely unilateral defects. Second, defects caused by tumor emboli generally do not resolve with time. **Left-sided** tumor emboli may result in visceral infarction, limb ischemia, myocardial infarction, or transient ischemic attack/stroke. In addition, multiple vascular aneurysms may develop. Of the benign primary cardiac tumors, embolization is most frequently noted with cardiac myxomas and even more so if the tumor has a villous surface. The brain is the most common site for systemic embolization in primary cardiac neoplasms, involving both hemispheres in approximately 40% of cases. Embolic findings in a young

person, in sinus rhythm and without valvular disease or endocarditis, should raise suspicion for the presence of an embolic source related to an intracardiac tumor.

- C. **Direct cardiac invasion/mass effect.** Signs and symptoms are governed by tumor location and size. Intramyocardial tumors, which are most often found in the left ventricular free wall and intraventricular septum, generally remain asymptomatic when the tumor size is small but can result in arrhythmias, conduction abnormalities, and sudden cardiac death if they become larger. Impaired ventricular performance may mimic restrictive or hypertrophic cardiomyopathy. Rarely, ventricular rupture has been the initial presentation. Tumors of the left atrium, especially if mobile, may prolapse into the mitral valve, resulting in obstruction of atrioventricular (AV) blood flow. This results in signs and symptoms similar to mitral stenosis, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, edema, and fatigue. Importantly, **syncope and sudden death** may also occur.

III. **PHYSICAL EXAMINATION.** Physical examination may show signs of pulmonary venous congestion. A fourth heart sound (S_4) may be present, as may a widely split, **loud first heart sound** (S_1). The loud S_1 is caused by late closure of the mitral valve, when the left ventricular–left atrial pressure crossover occurs at a higher pressure. Although this finding is also seen with mitral stenosis and preexcitation, the absence of a diastolic rumble or a short PR on an electrocardiogram should raise the possibility of left atrial tumor. Left atrial tumor may cause a holosystolic murmur at the apex radiating to the axilla (if tumor causes mitral incompetence) as well as diastolic murmur if the tumor obstructs mitral outflow. If the tumor obstructs the AV valve, a **presystolic crescendo murmur** may be present, which typically begins during ventricular systole as the tumor moves through the mitral orifice. This finding is present in approximately one-half of all patients with myxoma. The pathognomonic **tumor plop** manifests as an early diastolic sound, after an opening snap but before a third heart sound (S_3). Tumors of the **right atrium** often result in systemic venous congestion. Once significant pulmonary hypertension occurs, **systemic hypoxia, clubbing, and polycythemia** may develop as a result of right-to-left shunting. Right atrial tumors and intracavitary **right ventricular** tumors may present as right heart failure. A diastolic rumble that varies with inspiration may be noted and is due to tricuspid valve obstruction. The P_2 is delayed and may have varying intensities. Jugular venous pressure waveform examination may demonstrate **prominent a waves and Kussmaul's sign**. Recurrent pulmonary emboli can potentiate pulmonary hypertension. **Left ventricular** tumors, when not intramural, typically result in signs and symptoms of pulmonary venous congestion or low-output states. Upon examination, findings may mimic aortic stenosis, subvalvular stenosis, or hypertrophic cardiomyopathy.

IV. **DIAGNOSIS.** Because no clinical sign or symptom is specific, more advanced diagnostic methodology is universally required.

- A. **Electrocardiography (ECG).** In isolation, ECG provides little added clue to the diagnosis. However, changes in rhythm or voltage or development of new AV block on serial tracings may be the first sign of either extension of a primary cardiac tumor or development of secondary cardiac involvement.
- B. **Radiography.** Chest radiography may be helpful in identifying epicardial tumors. Cardiomegaly, mediastinal widening, or cardiac silhouette irregularities may suggest the diagnosis. Calcifications are seen occasionally. Pulmonary congestion or oligemia may be noted in patients with large left or right intracavitary tumors, respectively.
- C. **Echocardiography.** M-mode and two-dimensional echocardiography help establish the diagnosis in most patients. If a tumor is strongly suspected or a mass is noted by transthoracic echocardiography (TTE), transesophageal echocardiography (TEE) should be performed. TEE provides improved sensitivity (97% vs. 93% for TTE) and specificity, particularly with atrial masses, and allows for superior visualization of

anatomic details, such as contour, cysts, calcification, and presence of a stalk. Three-dimensional echocardiography is also increasingly helpful in evaluation due to its ability to visualize complex cardiac masses.

- D. **Radionuclide imaging.** Although gated blood pool scanning has been used to identify cardiac tumors in the past, the inferior resolution and sensitivity have made this form of imaging uncommon in the workup. Positron emission tomography scanning is useful in identifying cardiac involvement in metastatic tumors and atrial myxomas.
- E. **Computerized tomography (CT).** CT, especially multislice CT with contrast, is often used in the diagnosis and evaluation of cardiac masses. It can define tumor extension, although not as effectively as cardiac magnetic resonance (CMR), assess tumor calcification, and evaluate the adjacent extracardiac structures (pericardium and great vessels).
- F. **Cardiac magnetic resonance.** Like CT, CMR has an important role in the evaluation of cardiac tumors. Specifically, it characterizes size, shape, and surface features, as well as evaluating tissue composition—giving information regarding the type of tumor that is present. Magnetic resonance imaging (MRI) has the highest soft tissue contrast of the imaging modalities, and it is particularly helpful in distinguishing thrombus from tumor. It is also the most sensitive imaging modality for detecting the extent of tumor infiltration.
- G. **Angiography.** Cardiac catheterization is **not necessary in most cases**. However, in the following scenarios, the risk and cost of angiography may be worthwhile: clarifying inadequate noninvasive imaging, defining blood supply for suspected malignant tumors, and evaluating coexistent valvular or coronary artery disease that could alter surgical approach. The major additional risk of angiography is embolization of tumor or thrombus. A transseptal approach is relatively contraindicated in cases of suspected left atrial myxoma, given the high frequency of involvement of the fossa ovalis and the accompanying risk of embolization.
- H. **Endomyocardial biopsy (EMB).** Limited data exist on the utility of EMB in the management of cardiac tumors. Generally, diagnosis is made from noninvasive imaging; however, EMB can be considered if imaging is equivocal or if a tissue sample is required prior to treatment decisions (i.e., chemotherapy).

V. PRIMARY CARDIAC MALIGNANCIES

- A. **Benign neoplasms.** A description of specific benign cardiac tumors is given in subsequent text. Relative proportions are given in Table 41.1.
 - 1. **Myxomas.** Most benign cardiac tumors are myxomas, accounting for approximately 30% to 50% in most series. For **sporadic myxomas**, which account for nearly 90% of all myxomas, about 65% of patients are female, with a mean age of 56 years. Eighty-six percent of sporadic myxomas are found in the left atrium and 90% are solitary masses. When multiple tumors are present, they are not necessarily limited to one chamber. The typical site of attachment within the left atrium is on or near the **fossa ovalis**. It is important to note that **tumors located on the posterior wall of the left atrium are usually not benign**. Less frequently, myxomas may be found in the right atrium, either ventricle, or arising from the AV valves. **Familial myxomas** comprise 4.5% to 10% of all cardiac myxomas. Although pathologically identical to sporadic myxomas, they have a number of unique clinical features. They have a well-characterized **autosomal dominant** transmission. They are often present within the construct of a larger syndrome. The **Carney complex**, or “syndrome myxoma,” consists of both cardiac and noncardiac myxomas, spotty pigmentation (i.e., pigmented nevi), and endocrine overactivity (pituitary, adrenocortical, and endocrine testicular tumors). This may account for up to 7% of all cardiac myxomas. Patients with the Carney complex typically present in the third decade, often have bilateral tumors, and have high recurrence rates following resection. If a myxoma

TABLE 41.1 Relative Proportion of Benign and Malignant Tumors in Adults by Tumor Type

Benign tumor	% of group	Malignant tumor	% of group
Myxoma	46	Angiosarcoma	33
Lipoma	21	Rhabdomyosarcoma	21
Papillary fibroelastoma	16	Mesothelioma	16
Rhabdomyoma	2	Fibrosarcoma	11
Fibroma	3	Lymphosarcoma	6
Hemangioma	5	Osteosarcoma	4
Teratoma	1	Thymoma	3
AVN mesothelioma	3	Neurogenic sarcoma	3
Granular cell tumor	1	Leiomyosarcoma	1
Neurofibroma	1	Liposarcoma	1
Lymphangioma	1	Synovial sarcoma	1

AVN, atrioventricular nodal.

syndrome is suspected, **screening echocardiography is recommended** for all first-degree relatives, particularly if the index patient is young, has multiple tumors, or has typical noncardiac features of the genetic syndrome.

Pathologically, cardiac myxomas may be either smooth, round or gelatinous, or friable and irregular in appearance. They sometimes contain a hemorrhagic core and may attach via a sessile or pedunculated base. The typical diameter at presentation is 4 to 8 cm and the typical mass is 15 to 180 g. **Histologically**, myxomas have characteristic patterns of “lipidic” cells within glycosaminoglycan-rich myxoid stroma. **Ultrastructurally**, myxoma cells resemble embryonic mesenchymal cells. **Immunohistochemically**, they demonstrate variable activity for endothelial cell markers, with reliable positivity to vimentin, indicating a mesenchymal derivation. Myxomas also produce vascular endothelial growth factor, likely contributing to angiogenesis and tumor growth.

- 2. Lipomas.** These benign tumors occur at **all ages**, with men and women affected equally. Tumors range in size depending on their location. Seventy-five percent of tumors are found in the subendocardium, whereas the remainder are subepicardial, intramuscular, or valvular. Many tumors are **clinically silent** and identified only at autopsy. Subendocardial tumors may result in symptoms related to cavity obstruction, whereas subepicardial tumors can lead to compression of the heart and/or development of pericardial effusion. Intramyocardial tumors may result in arrhythmias or conduction disturbances and possibly sudden death. Valvular lipomas can lead to valvular insufficiency and heart failure. Lesions are generally **well encapsulated** with a center of predominantly benign fatty cells. Without pathologic confirmation, lipomas can be confused with lipomatous hypertrophy of the interatrial septum. Both MRI and CT are useful in diagnosing cardiac lipomas based on the characteristic features of fatty tissue with these techniques.
- 3. Papillary fibroelastomas.** The diagnosis of papillary fibroelastoma has increased with the more frequent use of TEE. They are the second most common primary cardiac tumors in adults and, grossly, these benign tumors resemble sea

anemones, with frondlike arms protruding off a central stalk. They are usually about 1 cm in length, single, and mobile in 40% of cases. The majority are located on the **ventricular surface of the aortic valve**, whereas the atrial side of the mitral valve is the second most common location. Rarely, they may present on the endocardial surfaces. Although these tumors are not associated with valvular dysfunction, in approximately 30% of cases, thrombus, with subsequent emboli, develops. Surgical resection is generally recommended for patients with a symptomatic presentation with embolization or in an asymptomatic patient with large, mobile tumors (1 cm or greater in diameter). Anticoagulation may be considered if recurrent embolization occurs in a nonsurgical candidate. Fibroelastoma may be differentiated from Lambl's excrescences by their location on noncontact areas of the valve.

4. **Rhabdomyomas.** Rhabdomyomas, the most common benign tumor in **children and infants**, are frequently located within one of the ventricles. These tumors are nearly always **multiple**, and the majority of patients have at least one intracavitary, obstructing lesion. The most common presentation for this type of cardiac tumor in adults is arrhythmia; however, it may be clinically silent if the tumors are small. There is a clear association with **tuberous sclerosis**: 80% of rhabdomyoma patients have the disease and 60% of tuberous sclerosis patients have rhabdomyomas. In some cases, rhabdomyomas may regress spontaneously during childhood.
 5. **Fibromas.** Generally, fibromas are found in **pediatric** populations as well; these benign connective tissue tumors are almost universally **intramural**. They are usually firm, circumscribed but unencapsulated, and may grow to **several centimeters**. They have preponderance for the left ventricle and unlike rhabdomyomas do not spontaneously regress. The **Gorlin's syndrome** includes cardiac fibromas, multiple basal cell carcinomas, jaw cysts, and skeletal abnormalities.
 6. **Hemangiomas/lymphangiomas.** These tumors are **very rare** and consist of benign collections of endothelial cells. Usually they are located within the intra-ventricular septum or AV node and as such may present as heart block, sudden cardiac death, or hemopericardium.
- B. Malignant neoplasms.** Histologically, **primary malignant tumors are virtually always sarcomas**. Suggestive **characteristics** include rapid growth, mediastinal invasion, hemorrhagic pericardial effusion, precordial pain, and pulmonary vein extension. Primary malignant neoplasms make up approximately 15% of all primary cardiac tumors.
1. **Angiosarcomas.** Almost always found within the right atrium, angiosarcomas, which include Kaposi's sarcoma, have a **2:1 male-to-female predilection** and are almost exclusively seen in adults. Hemorrhagic pericardial effusions are not uncommon. These tumors have ill-defined vascular channels lined with atypical endothelial cells. The blood flow through the tumor may produce a continuous precordial murmur. Despite resection and/or adjuvant therapy, clinical deterioration is rapid.
 2. **Rhabdomyosarcoma.** Like angiosarcomas, these tumors of striated muscle are **more common in men**. However, there is no specific chamber that is preferentially affected. Tumors are generally infiltrative, but on occasion they may develop polypoid extensions, which can cause them to be mistaken for myxomas. Prognosis is poor.
 3. **Mesothelioma.** The typical location of primary cardiac mesothelioma is the **pericardium**. Generally very diffuse, these tumors lead to symptoms consistent with pericarditis or hemorrhagic effusion. They may occasionally infiltrate the **AV node**, leading to conduction disturbances, sudden cardiac death, or tamponade. Much like cardiac sarcomas, these tumors carry a very poor prognosis.

4. **Other.** Fibrosarcomas, lymphosarcomas, liposarcomas, and other undifferentiated sarcomas represent the remainder of primary cardiac malignancies. These tumors are very rare and are generally infiltrative, involving multiple cardiac chambers. A clinical syndrome mimicking hypertrophic cardiomyopathy has been observed.

VI. SECONDARY CARDIAC MALIGNANCIES. As mentioned previously, most malignancies of the heart are secondary and, by definition, **metastatic**. The overwhelming majority of metastatic cardiac tumors occur in the **pericardium** and are usually **carcinomas**, as opposed to sarcomas. Due to increased prevalence, **the most commonly found metastatic tumor to the heart is lung cancer**. The typical presentation is of pericardial effusion or tamponade or pulmonary vein obstruction from direct extension. After metastatic lung cancer, breast cancer, lymphoma, leukemia, and renal cell carcinoma are the most common offenders. The tumor with **the greatest propensity to metastasize to the heart is melanoma**, followed by germ cell tumors and leukemia (Table 41.2). A new complaint referable to the heart in a patient with known extracardiac malignancy should prompt a thorough investigation to rule out cardiac malignancy. Unfortunately, prompt diagnosis usually does not favorably alter the prognosis.

VII. DIFFERENTIAL DIAGNOSIS. Establishing the correct diagnosis is imperative. A thorough differential diagnosis of **nonmalignant conditions** must be considered and ruled out. Possibilities include pericardial cysts, teratomas, lipomatous hypertrophy of the interatrial septum, thrombus, and sarcoid. Unfortunately, the final diagnosis in many cases must still be made pathologically.

VIII. THERAPY AND PROGNOSIS. The primary therapy for benign tumors remains **operative resection**, given the associated risk of lethal obstruction, arrhythmia, or embolization. Most surgeons perform excision with extracorporeal circulatory support in order to directly visualize the tumor, as well as a careful search for metachronous tumors. In higher risk patients, more extensive resection is recommended. The femoral or azygous vein is usually cannulated, as opposed to the right atrium, to avoid potential

TABLE 41.2 Metastatic Tumors to the Heart by Absolute Number and Greatest Propensity

Primary tumor	Absolute no.	Primary tumor	No. per 100 tumors
Lung	180	Melanoma	46
Breast	70	Germ cell	38
Lymphoma	67	Leukemia	33
Leukemia	66	Lymphoma	17
Esophagus	37	Lung	17
Uterus	36	Sarcoma	15
Melanoma	32	Esophagus	13
Gastric	28	Kidney	11
Sarcoma	24	Breast	10
Oral	22	Oral	9
Colon	22	Thyroid	9

tumor fragment embolization. Mitral valve repair or replacement is usually unnecessary in the absence of associated bacterial endocarditis. An analysis reviewing 106 operations for sporadic atrial myxomas noted only one perioperative death. Survival at 25 years is no different when compared with age- and sex-matched controls. There are limited data regarding the use of a minimally invasive or robotic approach to cardiac tumor resection. Small series suggest that parasternal or partial sternotomy access does not compromise the safety or efficacy while allowing for shortened hospitalization and better cosmetic results. Long-term follow-up is not yet available for this approach.

Regardless of the type of surgical resection or whether the tumor is sporadic, annual **follow-up noninvasive imaging is recommended** in all patients after resection. Recurrence rates of 12% to 22% have been quoted in patients with family histories, syndromes, and multiple tumors at original presentation versus 1% for patients with sporadic, isolated myxomas. Primary malignant tumors generally portend dismal prognoses. They are rarely cured by surgery because of the large amount of cardiac tissue involved. Adjuvant therapy (i.e., chemotherapy and radiation) after resection does not affect the prognosis, although it may slow progression in individual cases. **Palliative resection** is advocated for obstructive symptoms. **Cardiac transplantation** has been performed for patients with both benign and malignant tumors, but thus far, series have been too small to reliably predict outcomes.

ACKNOWLEDGMENTS: *The author would like to thank Drs. Adam W. Grasso and Nitin Barman for their contributions to earlier editions of this chapter.*

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Common Genetic Issues in Cardiovascular Disease

Genetic abnormalities have been associated with all types of cardiovascular disease, including coronary atherosclerosis, rhythm disorders, aortic disease, and structural heart disease. Since the initial descriptions of familial hyperlipidemia (FH) and the mutations in the low-density-lipoprotein (LDL) receptor (LDL-R), genetic studies have fostered an improved understanding of the underlying pathophysiology of various cardiovascular disease states. Furthermore, the sequencing of the human genome has ushered in the era of cardiovascular genomics. The ability to efficiently scour through the massive amount of genomic information will ultimately result in an improved understanding of the contributions of genetics to cardiovascular disease.

This understanding would potentially lead to an improved ability to accurately diagnose disease, prevent progression, and risk stratify at the individual level. Furthermore, this information will add to our understanding of the relationship between DNA variants and the response to drugs or other treatment modalities. The pharmacogenomic profiles developed may provide a refined approach to treatment with less toxicity. A more comprehensive assessment of future risk for both patient and potentially affected family members would also be feasible.

Although there are some examples within cardiovascular disease of simple monogenic disorders explained by principles of Mendelian inheritance, many of the entities, such as coronary atherosclerosis, acute myocardial infarction (MI), and atrial fibrillation (AF), are complex traits with multiple genes contributing to the phenotype. As opposed to Mendelian disorders, which are deterministic, complex traits are probabilistic.

It will require extensive time and effort to be able to define all the variations in all the genes that contribute to the susceptibility to or protection from a complex trait. Furthermore, the simple identification of genes involved does not address the issue of gene–gene and gene–environment interactions influencing complex traits. There have been extensive recent reports of genomic variants associated with risk of diseases. These variants are common, often accounting for 20% to 30% of the population attributable risk, but with an odds ratio of 1.2 or 1.3, for example, only 20% to 30% excess risk. These are common variants for common diseases. The hunt to find rare variants that induce susceptibility to common diseases with high risk (or protection) will be more challenging, but eminently feasible with sequencing technology and ultra high-throughput genotyping. At some point in the future, the major genomic underpinnings for most cardiovascular diseases will be known. Furthermore, the integration of all of the genomic variants for any cardiovascular disease has not been undertaken. What follows is a brief overview of what is known today about the genetic basis for a sampling of disease entities within cardiovascular medicine.

METHODOLOGY. The process of discovering relevant genetic underpinnings of generally complex traits requires an extensive analysis of genetic information in large populations. Complex traits without simple Mendelian patterns of inheritance are difficult to analyze, given that there are often multiple genes involved, with many gene interactions being important. However, even before attempting this task, perhaps the single most significant goal is to accurately and concisely define the phenotype in question. In addition, many variations

often exist within a single category of cardiovascular diseases such as hypertrophic cardiomyopathy (HCM) and acute MI. The ability to clearly define cases and controls is paramount to obtaining accurate and reproducible information.

There are three major methods of identifying DNA variants associated with cardiovascular disease. Of note, some of the single nucleotide polymorphism (SNP) variants that have been found are not in a gene, but actually in areas of the genome not associated with gene expression. It is not yet known how these variants exert their effect. Of note, the major variants for MI (at 9p21) and AF (at 4q25) fall into this category of intergene (i.e., not in a gene).

I. GENOME-WIDE ASSOCIATION STUDIES. Gene association studies utilize the concept that multiple SNPs, where a single nucleic acid substitution results in a different allele, can affect the risk of developing a disease in question. This is especially true in diseases of complex traits such as coronary artery disease (CAD) and MI. Using genes of interest in a particular disease phenotype, scans are conducted in areas of interest in both cases and controls to compare haplotype frequency to determine if a statistically significant difference between the two groups in the region of interest exists. One of the limitations of this technique is the inability to know whether the SNP of interest is involved in the pathogenesis or simply associated (in linkage disequilibrium) with another SNP that may actually be involved in the process. Utilizing this process of gene association across the entire genome is now possible with high-throughput sequencing technology of up to 1 million SNPs assessed per individual and the term “genome-wide” association has been coined. The SNPs assessed are tagging tiny bins of the genome, such that in a genome of an individual of European ancestry, there are only about 250,000 bins, most of which are sampled by current high-throughput genotyping. Each bin is typically inherited as a block (haplotype). The breakdown of the genome into bins via the International Haplotype map was critical in making current genome-wide association studies possible.

II. LINKAGE ANALYSIS. Linkage analysis is another tool used to identify genes that are possibly involved in the pathogenesis of complex traits. The use of linkage analysis begins without any assumptions as to the potential involvement of various genes. It is based on the idea that during the process of meiosis when recombination events occur, they tend to involve loci on a particular chromosome that are closer together than farther apart. By following the inheritance of certain known loci, assumptions can be made about the presence of alleles that cosegregate with them. Using linkage analysis, the potential exists to identify these known loci as markers and determine the transmission through a pedigree and its relationship to the phenotype in question. In doing so, it may be possible to suggest that an allele in proximity to known loci may be associated with a particular phenotype. The logarithm of odds ratio (LOD score) is used to estimate the (distance) relationship between the known locus of interest and an unknown locus thought to be associated with the disease phenotype. A LOD score of 3 is used to classify such a statistically meaningful linkage.

III. GENE EXPRESSION PROFILING. The identification of certain disease alleles or loci associated with disease-causing genes provides valuable information but remains limited in its scope. The statistical association of genes and disease **does not prove causation or even involvement** in disease. Gene expression profiling takes this concept one step forward in trying to delineate gene expression. The presence of transcription profiles may provide more useful information in terms of relevance of findings made in gene association studies or linkage analysis. Technology now permits the evaluation of large genomes in a rapid fashion to derive expression profiles, which can then be compared between diseased and healthy individuals to draw conclusions about which genes are transcriptionally active in certain phenotypes.

A. Coronary atherosclerosis and atherothrombosis. Coronary atherothrombosis and atherosclerosis remain significant causes of morbidity and mortality in the population as a whole. There is a great deal of variation in presentation in atherosclerosis and in acute MI. The presence of atherosclerosis is necessary but not sufficient

for atherothrombosis. There are separate factors involved that predispose to plaque rupture and thrombosis. Even within the category of plaque rupture, the clinical phenotypes vary significantly, as reflected by the spectrum of diseases that constitute the acute coronary syndromes. These entities are complex traits and are influenced by multiple pathways. Inflammation, endothelial dysfunction, and dyslipidemias are only a few of the pathways influencing the development of atherothrombosis and atherosclerosis. Delineating the genetic basis, in most cases, is a work in progress, but it may help to broaden our understanding of the disease.

1. Dyslipidemia: familial hyperlipidemia and other genetic variants. Dyslipidemia is a known risk factor for the development of atherosclerosis. Familial hyperlipidemia (FH) is a well-characterized, albeit relatively uncommon, entity defined by elevated levels of serum LDL levels, which predispose to coronary atherosclerosis. Often, these patients can develop atherosclerotic disease between 20 and 30 years of age. In FH, the dyslipidemia is often severe and not responsive to standard lifestyle and pharmacologic interventions.

- a. Autosomal dominant.** The underlying problem in this form of FH has to do with an abnormality in the clearance of the *LDLR* gene, and, as a consequence, elevated levels of LDL persist. The *LDLR* gene located at 19p13.2 has approximately 1,600 known mutations, and these appear to affect many aspects of LDLR function. Alterations in the gene range from point mutations to gene rearrangements. homozygotes and heterozygotes for FH vary in terms of the severity of lipid levels. The majority of individuals are heterozygous, and those with homozygous patterns of inheritance are more severely affected. Typically, these patients and affected family members develop premature coronary atherosclerosis and MI.
- b. Autosomal recessive.** This occurs as a result of a mutation in the low-density-lipoprotein receptor adaptor protein 1 (*LDLRAP1*) gene at 1p36-p35. The phenotype of this form of FH is milder than the autosomal dominant form of the disease and more amenable to treatment with lipid-lowering agents.
- c. Familial defective apolipoprotein B.** The cellular mechanisms involved in cholesterol metabolism are complex, and there are many potential targets where mutations can significantly affect phenotype. One such example is a point mutation in the apolipoprotein B (apo B) component of the LDL molecule. The Arg3500Gln is the most common substitution in the apo B (*APOB*) gene and results in the inability of LDL to bind to its LDLR. This mutant allele is more common in Northern European populations as a cause of hyperlipidemia, but the phenotype appears to be less severe than in the familial hyperlipidemia caused by *LDLR* mutations.
- d. Proprotein convertase subtilisin/kexin type 9 (*PCSK9*).** Less than 5% of FH involves *PCSK9* gene, located at 1p32.3, responsible for increasing degradation of the LDL receptor. Mutations in *PCSK9*, such as D374Y, F216L, S127R, D129N, D374H, N425S, and R496W, confer gain in function and cause FH. Much rarer *PCSK9* mutations are those that result in loss of function and act to reduce serum cholesterol levels, thereby conferring a protection against coronary atherosclerosis. Many new *PCSK9* mutations have been identified, but their effect on *PCSK9* functions requires further investigation.

In addition to the FH syndromes, there is a multitude of genes involved in more frequently occurring types of dyslipidemia. Phenotypically, these forms of dyslipidemia are less severe and more amenable to treatment than those observed in the FH population.

2. Endothelial function. *MEF2a* is a transcription factor that localizes to the endothelial cell of coronary arteries and is believed to be important in the function of endothelial cells. In 2003, a mutation in the *MEF2a* gene was described in a large family with autosomal dominant transmission of coronary atherothrombosis.

A 21-bp deletion in exon 11 was thought to result in loss of function. Three additional variants in the *MEF2A* thought to be associated with MI and CAD have also been reported. The findings from a large Spanish case-controlled study provided supporting evidence for only one of these variants, P279L. Further studies have failed to replicate these mutations in association with MI. The 21-bp deletion has not been found in any family apart from that in the original study. This particular mutation may be a “private mutation” for the family in the original study and therefore extremely difficult to replicate. In 2008, Lieb et al. (1) conducted a large German study, with 23 MI families, > 1,700 MI patients, and 2 large control populations, and did not find any evidence that the *MEF2A* gene had any linkage or association with MI/CAD.

3. **Inflammation.** The genes *ALOX5AP* (arachidonate 5-lipoxygenase-activating protein) and *LTA4H* (leukotriene A4 hydrolase) encode proteins involved in the leukotriene pathway, particularly in the synthesis of the proinflammatory leukotriene B mediators. The case for inflammation as a significant participant in acute MI has been made stronger by the discovery, through linkage analysis to a locus at 13q12-13, of a four SNP haplotype (Hap A) in the gene *ALOX5AP*. Carriers of the variant had higher levels of leukotriene B4. This variant was found to double the risk of MI and to almost double the risk of stroke. Another haplotype variant (Hap B) of the *ALOX5AP* gene was found to confer a doubling of the risk of MI in a British cohort. In Italy, researchers identified an increased risk for CAD with Hap B only. In a large German study, presence of the haplotype B indicated an association with an increased risk of MI. These studies provide strong evidence of the role of *ALOX5AP* gene for increased CAD risk in Europeans. In a case-control study of a US Midwestern population with European American ancestry, seven SNPs in the *ALOX5AP* gene along with two haplotypes (Hap A and Hap B) were genotyped. The results indicated that Hap B and one of the SNPs (SG13S377) were significantly associated with increased risk of premature CAD. In a meta-analysis conducted in 2010, the Hap B and SNP (rs1722842) variants in the *ALOX5AP* gene were associated with coronary heart disease, while Hap A was associated with the risk of MI.

The *LTA4H* gene encodes leukotriene A4 hydrolase and is also involved in the inflammation pathway. A haplotype (HapK) in the *LTA4H* gene moderately increased the risk of MI in a cohort from Iceland. A moderate risk was also found in studies of three US cohorts with European Americans, but HapK, although rarer in African Americans, tripled their risk of MI. The results of these studies with the *ALOX5AP* and the *LTA4H* variants provide the basis for further research to develop new drugs targeting the leukotriene pathway, thereby preventing or reducing the risk of MI and CAD in the future.

- B. **Connective tissue abnormalities and disease of the aorta.** Genetic mutations affecting the connective tissue and extracellular matrix typically affect multiple organ systems, but often the most devastating and lethal effects arise from those upon the cardiovascular system. Aortic dissection and rupture are often the consequences of such abnormalities, and what follows is a brief description of three such disorders.

1. **Marfan syndrome.** This disorder is inherited in an autosomal dominant fashion with variable penetrance, and it affects the connective tissue, leading to abnormalities of organs of the cardiovascular, skeletal, and ocular systems. The genetic defect is in the **fibrillin-1 (*FBNI*) gene on chromosome 15q21**. Often, the diagnosis is made on clinical grounds alone. The classic features of tall stature, arachnodactyly, dolichostenomelia, pectus excavatum, ectopia lentis, and a positive family history all support a diagnosis of Marfan syndrome. The cardiovascular system is affected, and the most common cause of death in these patients is from aortic dissection and aortic rupture. Other common related problems include aortic dilation, aortic valve regurgitation, mitral valve prolapse (MVP), tricuspid valve prolapse, and arrhythmias. When patients with Marfan syndrome present with dissection, they are typically younger and do not have hypertension.

The *FBNI* gene is responsible for producing a key constituent of microfibrils, which are important in the extracellular matrix. Microfibrils add to the elastic properties of extracellular tissue. Over 1,000 mutations in the *FBNI* gene have been recognized and appear to affect different aspects of cellular processing of fibrillin-1. These mutations can vary from a SNP to a premature stop codon. There are no specific relationships between mutations and phenotypes as of yet. Family members with Marfan syndrome and **the same *FBNI* gene mutation may show wide variation in onset and severity of cardiac symptoms**. The diagnosis of Marfan syndrome is generally made on a clinical basis. However, genetic testing for Marfan syndrome is available.

2. **Ehlers-Danlos syndrome.** Ehlers-Danlos syndrome is a group of connective tissue disorders caused by defects in proteins that are involved in the formation of collagen. It is uncommon and has an autosomal dominant pattern of inheritance. There are multiple types of Ehlers-Danlos syndrome based on the collagen type affected; however, the cardiovascular system is involved prominently in type IV, the vascular type of Ehlers-Danlos syndrome. The gene, ***COL3A1*, involved in this subtype is localized to chromosome 2q24.3-q31 and encodes for type III procollagen**. Vascular complications include dissections of the carotids and the vertebral arteries. Aortic dissections are the primary cause of death and often involve both the thoracic and the abdominal aortas. Diagnosis is usually ascertained clinically along with genetic testing for evidence of the mutation in the *COL3A1* gene.
 3. **Loeys-Dietz syndrome.** Loeys-Dietz syndrome is a connective tissue disorder characterized by hypertelorism, cleft palate, and vascular disease in the form of arterial aneurysms and dissection. It is inherited in an autosomal dominant pattern. Clinically, these patients are at high risk for aortic dissection. Loeys-Dietz syndrome is caused by **mutations in the transforming growth factor beta (*TGF-β*) receptors I and II genes (*TGFBR1* and *TGFBR2*) on chromosome 3**. Phenotypically, the characteristics are like those in Marfan syndrome, and also these patients appear similar (with the exception of the craniofacial abnormalities) to Ehlers-Danlos patients with vascular involvement (type IV). The relevance of this distinction is that those with Loeys-Dietz appear to have much lower intraoperative mortality during corrective vascular surgery. Genetic testing to identify the mutation is needed for definitive diagnosis, but it is not available in all laboratories.
- C. Cardiomyopathies.** Primary disease of the myocardium affects both systolic and diastolic function and often results in heart failure or other adverse events over time. Many of the nonischemic cardiomyopathies have a strong genetic component to explain their phenotype. Perhaps, the most clinically relevant entities include dilated cardiomyopathy (DCM) and HCM. Cardiomyopathies can also occur as a secondary process in response to a separate unrelated factor (i.e., hypertension), and it is unknown to what degree genetic susceptibility determines the myocardial response/remodeling over time. Until recently, the classification of cardiomyopathies has been based on the phenotype and morphologic characteristics. However, with an improved knowledge of the genetics of these disorders, a new understanding and appreciation for the underlying mechanisms of disease in these disorders will undoubtedly influence how these entities are treated in the future.
1. **Dilated cardiomyopathy.** DCM is characterized by dilation of one or both of the ventricular chambers resulting in severe systolic dysfunction and characterized by congestive heart failure. A genetic cause is thought to account for 20% to 50% of DCM cases, and in many cases, the pattern of inheritance is autosomal dominant. However, recessive, X-linked, and mitochondrial patterns of inheritance are also seen. Many cases of DCM are secondary to other etiologies. Mutations in more than 30 genes have been associated with this phenotype, and although the products of most of these genes are important structural proteins, there are others involved in the handling of calcium and regulation of energy within the myocytes. Again, however, there are often subtle differences in the

various types of DCM, such as age of onset and degree of clinical symptoms, all of which may suggest separate genetic abnormalities are at play. Mutations in the sarcomere protein genes account for approximately 10% of DCM. Mutations in *LMNA* gene, which encodes lamin A and lamin C, are seen in DCM with prominent conduction system disease. Although mutations in *SCN5A* are also associated with this type of DCM, the clinical picture differs as ventricular dysfunction is usually present. Dystrophin gene mutations are seen in X-linked DCM. Mutations in the *ALMS1* gene are transmitted in a recessive pattern, resulting in DCM with hearing loss. Genetic testing is available for many of the gene mutations that have been identified. Table 42.1 lists some of the genetic variants that are believed to be associated with various DCM phenotypes.

2. **Hypertrophic cardiomyopathy.** HCM (see Chapter 10) is a highly variable and heterogeneous disease process that affects the myocardium, with clinical manifestations varying from completely asymptomatic to severe (sudden cardiac death). The

TABLE 42.1 Genetic Variants Associated with Dilated Cardiomyopathy

Gene	Location	Mode of inheritance	Gene product and function
MYH7	14q11	Autosomal dominant	Sarcomere gene—encodes β -myosin heavy chain Mutations may affect contractile mechanism
MYH6	14q12	Autosomal dominant	Sarcomere gene—encodes α -myosin heavy chain Mutations may affect contractile mechanism
TNNT2	1q32	Autosomal dominant	Sarcomere gene—encodes troponin T type Mutations may affect contractile mechanism
ACTC1	15q11-q14	Autosomal dominant	Sarcomeric gene—encodes cardiac actin Vital part of contractile apparatus of myocyte
TMP0	12q22	Autosomal dominant	Encodes thymopoietin—maintains functional integrity of nucleus
CSRP3	11p15	Autosomal dominant	Encodes cardiac muscle LIM protein Functions as a stretch sensor in myocyte
Phospholamban (PLN)	6q22	Autosomal dominant	Controls muscle relaxation through calcium regulation via calcium ATPase
DES	2q35	Autosomal dominant	Encodes desmin—cytoskeletal protein involved in stabilization of sarcomere and mutation may affect contractile force
Presenilin (PSEN1/2)	14q24.3 (<i>PSEN1</i>) 1q31-q42 (<i>PSEN2</i>)	Autosomal dominant	<i>PSEN1</i> encodes presenilin 1 <i>PSEN2</i> encodes presenilin 2 Transmembrane proteins
Lamin A/C (LMNA)	1q22	Autosomal dominant	Encodes lamin A and lamin C Structural proteins—affect structure of nucleus in myocytes DCM with prominent conduction system disease
SCN5A	3p21	Autosomal dominant	Cardiac sodium channel gene DCM with prominent conduction system disease

TABLE 42.1 Genetic Variants Associated with Dilated Cardiomyopathy (Continued)

Gene	Location	Mode of inheritance	Gene product and function
Dystrophin (DMD)	Xp21.2	X-linked	Encodes dystrophin More commonly involved in Duchenne's and Becker's muscular dystrophy Mutations can affect transduction of contractile force X-linked DCM
ALMS1	2p13	Autosomal recessive	Alstrom syndrome 1 Causes with DCM and hearing impairment Encodes for protein associated with obesity and diabetes Autosomal recessive DCM

DCM, dilated cardiomyopathy.

broad range of phenotypes and significant selection bias resulted in an overestimation of the mortality rate associated with this disease. The clinical spectrum of the disease is wide, and the ability to accurately predict outcomes remains challenging. The clinical variability of HCM is not only limited to the presenting phenotype but also related to age of presentation, clinical course, and eventual outcomes, making it very challenging to properly identify a phenotype of interest. The characteristic phenotype is an asymmetrically hypertrophied myocardium with a small ventricular chamber and occasionally a left ventricular (LV) outflow tract (with systolic anterior motion of the mitral valve) and/or an intracavitary gradient.

More than 700 mutations in 13 separate genes have been identified, with the majority of mutations in 3 of the genes: *MYH7* on chromosome 14, *MYBPC3* on chromosome 11, and *TNNI2* on chromosome 1. The genes involved encode proteins of the cardiac sarcomere unit. The products of these genes involved include troponin T, troponin I, β -myosin heavy chain, myosin light chains, myosin-binding protein C, α -myosin light chain, α -tropomyosin, and actin.

The importance of properly characterizing a phenotype as heterogeneous as HCM has been illustrated by the example of glycogen storage diseases mimicking the appearance of HCM. Mutations in the genes for AMP-activated protein kinase gamma2 (*PRKAG2*) and lysosome-associated membrane protein 2 (*LAMP2*) were found in phenotypes that closely resembled HCM but were differentiated based on serum protein levels and ventricular preexcitation.

3. **Arrhythmogenic right ventricular cardiomyopathy/dysplasia.** Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a primary abnormality resulting in fibrofatty infiltration of the myocardium, primarily the right ventricle. Clinical manifestations include right ventricular dysfunction and lethal ventricular arrhythmias. Diagnosis often includes a battery of tests, including an electrocardiogram demonstrating repolarization abnormalities and an epsilon wave, magnetic resonance imaging or computed tomography demonstrating fibrofatty infiltration of the right ventricle, and endomyocardial biopsy. Often a positive family history of the disorder is present. ARVC/D can be inherited in either an autosomal dominant (in most cases) or autosomal recessive pattern. Mutations in 12 genes associated with ARVC/D have been identified. Mutations in genes encoding desmoplakin, desmoglein-2, cardiac ryanodine receptor, and plakophilin-2 have all been associated with the autosomal dominant form of the

disease. In ARVC12, mutations in the *JUP* gene, encoding junction plakoglobin, have an autosomal dominant pattern of inheritance, whereas mutations in the same *JUP* gene with an autosomal recessive inheritance result in Naxos disease, a variant associated with the triad of ARVC/D along with dermatological manifestations such as wooly hair and palmoplantar keratoderma. Twelve subtypes of ARVC/D are distinguished on the basis of the gene involved and are described further in Table 42.2.

4. **Left ventricular noncompaction.** Left ventricular noncompaction (LVNC) is a relatively rare congenital abnormality of the myocardium resulting in a trabeculated appearance of the LV cavity. It is characterized by spongy myocardium that results from arrest in endomyocardial morphogenesis. It is seen in < 1% of adults. This disorder can occur in isolation or in association with other congenital anomalies. Over time, it is thought that noncompaction can proceed to DCM with severe systolic dysfunction. Different genes are thought to be involved in the pathogenesis for each of the LVNC variants. A mutation in the α -dystrobrevin gene (*DTNA*) on chromosome 18 has been linked to left ventricular noncompaction-1 (LVNC1). A mutation for LVNC2 has been identified on chromosome 11p15 (LVNC2). LVNC3 is caused by mutation in the *ZASP* gene on chromosome 10q22.2-q23.3. LVNC variants have been mapped specifically to mutations of the sarcomere genes: LVNC4 is caused by mutation in the *ACTC1* gene (chromosome 15q14), LVNC5 is caused by mutation in the *MYH7* gene (chromosome 14q12), and LVNC6 is caused by mutation in the *TNNI2* gene

TABLE 42.2 Genetic Variants of ARVC/D

ARVC/D variant	Chromosome/ gene	Comments
ARVC/D1	14q23-24/ <i>TGFβ-3</i>	TGF β -3 involved in embryogenesis and cell differentiation
ARVC/D2	1q41.1-q43/ <i>RYR2</i>	Ryanodine receptor involved in Ca ²⁺ release into cytosol
ARVC/D3	14q12-q22	In 1996, discovered in a study of three small families
ARVC/D4	2q32.1-q32.3	Some family members from affected cohort had involvement of the left ventricle
ARVC/D5	3p25.1/ <i>TMEM43</i>	TMEM43 is a transmembrane protein expressed in blood and cardiac tissue
ARVC/D6	10p14-p12/ <i>PTPLA</i>	Protein tyrosine <i>phosphatases</i> involved in cell growth and <i>PTPLA</i> is primarily found in cardiac tissue
ARVC/D7	10q.22.3 2q35/ <i>DES</i>	
ARVC/D8	6p24/ <i>DSP</i>	Desmoplakin (DSP) is a constituent protein of desmosomes
ARVC/D9	12p11/ <i>PKP2</i>	Plakophilins are part of desmosomes and are also found in the nucleus regulating transcription PKP2 encodes plakophilin-2, an essential armadillo repeat protein of the cardiac desmosome
ARVC/D10	18q12.1-q12/ <i>DSG2</i>	Encodes for desmogleins involved in desmosome cell adhesion
ARVC/D11	18q12.1/ <i>DSC2</i>	Encodes for desmocollin, a desmosomal cadherin protein
ARVC/D12	17q21/ <i>JUP</i>	Encodes junctional plakoglobin/JUP

From OMIM Online Mendelian Inheritance in Man (<http://www.ncbi.nlm.nih.gov/omim/>).

(chromosome 1q32). There is also an X-linked form of LVNC (LVNCX) caused by mutation in the gene encoding tafazzin (TAZ) and allelic to Barth syndrome.

D. Arrhythmogenic disorders

1. **Brugada syndrome.** Disorders of the conduction system of the heart lead to significant clinical manifestations, most notably ventricular arrhythmias and sudden cardiac death. Two entities, long QT syndrome (LQTS) and Brugada syndrome, have been well described, and their respective genetic abnormalities have been characterized. Brugada syndrome was initially described by Josep and Pedro Brugada in 1992. Clinically, ventricular arrhythmias and sudden cardiac death occur, particularly in middle-aged men. Characteristic electrocardiographic features can help make the diagnosis, and, in some cases, certain drugs, including sodium channel blockers and tricyclic antidepressants, can unmask the abnormality on a surface electrocardiogram. **Brugada syndrome is typically inherited in an autosomal dominant pattern.** However, a de novo mutation can occur in approximately 1% of cases. Mutations in eight genes have been identified as causing Brugada syndrome: *CACNA1C*, *CACNB2*, *GPD1L*, *HCN4*, *KCNE3*, *SCN1B*, *SCN3B*, and *SCN5A*. The *SCN5A* gene has been mapped to chromosome 3p22.2 and is a voltage-gated sodium channel gene. *SCN1B* (chromosome 19q13.12) and *SCN3B* (chromosome 11q24.1) are also voltage-gated sodium channel genes. *GPD1L*, an NAD-dependent glycerol-3-phosphate dehydrogenase gene, is associated with chromosome 3p22.3. *HCN4*, on chromosome 15q24, is a hyperpolarization-activated cyclic nucleotide-gated potassium channel 4 gene. *KCNE3* (chromosome 11q13.4) is a voltage-gated potassium channel gene. *CACNA1C* (chromosome 12p13.33) and *CACNB2* (chromosome 10p12.33-10p12.31) are two subunits of the L-type voltage-dependent calcium channels. Genetic testing in Brugada syndrome is used to confirm a clinical diagnosis. A negative result does not necessarily exclude the diagnosis. It may reflect that the individual does not have the condition, but it may also mean that the individual either has a mutation in a gene not part of the testing panel or has a mutation in a Brugada-associated gene not included in the panel.
2. **Long QT syndrome.** LQTS encompasses a range of disorders characterized clinically by syncope and sudden cardiac death, with electrocardiographic abnormalities in the QT interval and in the T-wave morphology. LQTS is usually inherited in an autosomal dominant pattern. Recessive inheritance, seen in Jervell and Lange-Nielsen types 1 and 2, is rare. There are 12 different types of LQTS based on the type of gene involved. The various forms of LQTS are often distinguishable by clinical features and genetic abnormalities. One such distinguishing feature is that those with long QT syndrome 1 (LQT1) are typically at higher risk during periods of exercise, whereas those with the long QT syndrome 3 variant (LQT3) are at higher risk during sleep. The *KCNQ1* gene encodes the catecholamine-sensitive portion of the potassium channel responsible for conducting the delayed rectifier current (I_{Kr}) in the LQT1 variant, whereas the *SCN5A* gene is affected in the LQT3 variant. The underlying defect involving the sodium channel results in a prolonged depolarization current, whereas defects involving the potassium channel result in a longer QT duration secondary to inability to reestablish repolarization within the myocyte. The autosomal recessive phenotypes (Jervell and Lange-Nielsen types 1 and 2) are associated with bilateral sensorineural hearing loss.

Hundreds of mutations are believed to be involved in LQTS. However, most of the prognostic information available is based on the gene involved and not the specific mutation. Having the genotypic information can help in prognosis and in determining response to therapy. The rates of ventricular arrhythmias and sudden cardiac death vary based on the gene involved, as does the response to therapy. This information may be particularly helpful in trying to decide between medical therapy, implantable cardioverter-defibrillator implantation, or both. Table 42.3 lists the 12 variants of LQTS and the genes involved.

TABLE 42.3 Genetic Variants Associated with Long QT Syndrome

LQT variant	Gene	Mode of inheritance	Function of gene product
LQT1	<i>KCNQ1</i>	Autosomal dominant	Catecholamine-sensitive portion of I_K potassium channel
LQT2	<i>KCNH2</i>	Autosomal dominant	α -Subunit of I_{Kr} potassium channel
LQT3	<i>SCN5A</i>	Autosomal dominant	Cardiac sodium channel
LQT4	<i>ANK2</i>	Autosomal dominant	Ankyrin protein
LQT5	<i>KCNE1</i>	Autosomal dominant	β -Subunit of I_{Ks} potassium channel
LQT6	<i>KCNE2</i>	Autosomal dominant	β -Subunit of I_{Ks} potassium channel
LQT7	<i>KCNJ2</i>	Autosomal dominant	Subunit of I_{Kr} potassium channel
LQT8	<i>CACNA1C</i>	Autosomal dominant	Subunit of the L-type voltage-dependent calcium channel
LQT9	<i>CAV3</i>	Autosomal dominant	Encodes caveolin-3, which is found in the membrane surrounding muscle cells <i>CAV3</i> gene mutations may affect the function of sodium channels
LQT10	<i>SCN4B</i>	Autosomal dominant	β -voltage-gated sodium channel subunit
LQT11	<i>AKAP9</i>	Autosomal dominant	Encodes the A-kinase anchor protein-9
LQT12	<i>SNTA1</i>	Autosomal dominant	Syntrophin, alpha 1 peripheral membrane protein associated with dystrophin, and dystrophin-related proteins
Jervell and Lange-Nielsen type 1	<i>KCNQ1</i>	Autosomal recessive	Subunit I_K channel
Jervell and Lange-Nielsen type 2	<i>KCNE1</i>	Autosomal recessive	β -Subunit of I_{Ks} potassium channel

- 3. Atrial fibrillation.** AF is the most common of the arrhythmic disorders. The majority of adult-onset familial AF is inherited in an autosomal dominant pattern. A major breakthrough has occurred in the genomics of AF, with the finding that variants at **4q25 carry a risk of 1.6 and a population attributable risk of > 30%** in individuals of both European and Asian ancestries. The 4q25 variants are near a gene—*PITX2*—which is involved in left–right symmetry of the heart in development. It has not yet been proven how the variants at 4q25 exert their effect. Other genes contribute to a much smaller degree to the risk of AF. The majority of the mutations linked to AF have been found in the potassium ion channel genes (*KCNQ1*, *KCNJ2*, *KCNE2*, and *KCNH2*). The connexin 40 gene (*GJA5*) has also been implicated as a possible candidate. Due to the small number of mutations identified for familial AF, it is quite possible that there are many more mutations for familial AF that are still unknown. Genotype–phenotype correlations for familial types of AF have yet to be determined.

E. Valvular heart disease

1. **Mitral valve prolapse.** MVP (see Chapter 16) is a common disorder that appears to have a strong genetic component, and the familial form is likely inherited in an autosomal dominant pattern with variable penetrance. Although, in addition, it occurs in an idiopathic form, it is also associated with other valvular syndromes such as bicuspid aortic valve (BAV) and connective tissue diseases, which typically affect cardiovascular function such as Marfan syndrome, osteogenesis imperfecta, and Ehlers-Danlos syndrome. Prolapse of the mitral valve occurs primarily in the connective tissue matrix of the valve itself. Myxomatous degeneration of the valve tissue leads to redundant tissue and weakening of both the valve and the subvalvular apparatus. Clinically, this manifests as displacement of the mitral valve leaflets into the left atrium during systole and may progress to mitral regurgitation and eventual congestive heart failure with occasional rupture of the chordae. Although surgical repair and replacement have improved the long-term prognosis of this disorder, understanding the genetic basis of this disease may allow the earlier diagnosis and development of therapies to prevent progression.

Three genes have been identified with MVP inherited in an autosomal dominant manner. These are *MMVP1* (chromosome 16p12.1-11.2), *MMVP2* (chromosome 11p15.4), and *MMVP3* (chromosome 13q31.1-32.1). X-linked myxomatous valvular dystrophy (XMVD) has been mapped to chromosome Xq28, and the filamin A gene (*FLNA*) has been identified as a cause of XMVD. Filamin A may also have a role in MVP.

2. **BAV and aortic valve calcification.** Aortic valve disease (see Chapter 15) can be divided into two different types based on clinical characteristics: BAV and calcific aortic valvular disease. Calcific aortic valvular disease is typically a disease of the elderly and appears to be affected by those risk factors predisposing toward CAD. Vitamin D receptor polymorphisms have been implicated in the genesis of degenerative aortic valve disease, as has the apo E4 allele of the apolipoprotein E allele. BAV disease is believed to be a congenital abnormality that is typically discovered earlier on in life and is associated with disease of the aorta. What these two disorders have in common is the eventual progression to calcification of the aortic valve itself. Mutations in the *NOTCH1* gene on chromosome 9 have been implicated in BAV development. NOTCH1 is a transmembrane protein with transcriptional regulatory activity that is vital not only for aortic valve development but also for calcification. It is thought that mutations in this gene may allow the normally repressed transcription factor Runx2 to facilitate the development of valvular endothelial cells into osteoblastlike cells and promote valvular calcification. Mutations in the *ACTA2* gene on chromosome 10q23.3, which codes for actin, have also been linked to BAV. Mutations in ubiquitin fusion degradation 1-like gene (chromosome 22) have also been implicated in BAV. This gene codes for a signaling protein that is prevalent during embryonic formation of cardiac outflow tracts. Three additional loci associated with BAV have been identified on chromosomes 5, 13, and 18, but no specific genes have been discovered.

- F. **Inborn errors of metabolism.** Cardiovascular disease is often a manifestation of genetic abnormalities in separate pathways, which produce secondary effects upon the cardiovascular system. Many of these genetic mishaps occur in multiple pathways essential to metabolism, and their resultant phenotypes often impose upon the cardiovascular system. Table 42.4 lists some examples of metabolic abnormalities and the associated cardiac manifestations.

- G. **Chromosomal abnormalities and cardiovascular disease.** Chromosomal abnormalities that occur at the time of development can have serious implications with regard to the proper growth and development of a child. Although neuropsychiatric development is often delayed, the cardiovascular system is also affected in many of

TABLE 42.4 Cardiovascular Manifestations of Systemic Metabolic Disease

Metabolic disorder	Gene/protein defect	Effect upon cardiovascular system	Comments
Anderson-Fabry disease	α -Galactosidase deficiency	Accumulation of globotriaosylceramide Cardiomyopathy in the form of LVH, lethal arrhythmias, and coronary ischemia	X-linked
Hereditary hemochromatosis	<i>HFE</i> , an MHC class I-like protein, ferroportin, hepcidin, hemojuvelin, and transferrin receptor-2	Iron deposition involves the heart and results in cardiomyopathy	Can be acquired via transfusion-associated hemochromatosis
Niemann-Pick disease	Defect in sphingomyelinase	Accumulation of sphingomyelin in cardiac tissue leading to cardiomegaly	Affected children do not survive past first few years of life
Hurler's syndrome (type 1 mucopolysaccharidosis)	Deficiency in α -L-iduronidase	Biventricular enlargement, endocardial fibrosis, and valvular disease	Autosomal recessive
Hunter's syndrome (type 2 mucopolysaccharidosis)	Deficiency in iduronate sulfatase	Cardiac involvement includes valvular disease	X-linked
Danon disease	Deficiency in lysosome-associated protein type 2	Cardiac involvement includes LVH, CHF, and preexcitation	X-linked
Gaucher's disease	Deficiency of glucocerebrosides	Accumulation of glucocerebroside leading to cardiomyopathy, also calcification of aorta and aortic and mitral valves	
Pompe disease	Defect in glycogen storage	Biventricular concentric hypertrophy	Autosomal recessive transmission
L-Carnitine deficiency	<i>OC7N2</i> gene mutations affecting transport of carnitine	Cardiomegaly and dilated cardiomyopathy	Carnitine transport is vital for mitochondrial function. Cardioprotective benefits may be derived from protection from free radical damage

LVH, left ventricular hypertrophy; MHC, major histocompatibility complex; CHF, congestive heart failure.

TABLE 42.5 Common Chromosomal Abnormalities and Associated Cardiovascular Disease

Syndrome	Chromosomal abnormality	Associated CV abnormality
Down syndrome	Trisomy 21	Endocardial cushion defect, mitral valve prolapse, and tetralogy of Fallot
Turner syndrome	45X	Coarctation of the aorta, bicuspid AV, and anomalous PV return
Patau syndrome	Trisomy 13	Dextrocardia, ASD/VSD, and bicuspid AV
Edwards syndrome	Trisomy 18	PDA and left SVC
Fragile X syndrome	<i>FMR1</i> gene (X chromosome) with trinucleotide repeats	Mitral valve disease

CV, cardiovascular; ASD, atrial septal defect; AV, aortic valve; PV, pulmonary vein; PDA, patent ductus arteriosus; SVC, superior vena cava; VSD, ventricular septal defect.

these disorders and often survival may be limited due to the severity of congenital defects. Table 42.5 lists common syndromes associated with chromosomal structural abnormalities and the associated cardiovascular findings.

ACKNOWLEDGMENTS: *The authors acknowledge Dr. Eric Topol's contribution to an earlier version of this chapter.*

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SECTION

VIII

Preventive Cardiology

EDITOR

Leslie Cho

Dyslipidemia

- I. **INTRODUCTION.** Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in the industrialized world. It is estimated that 30% of all deaths worldwide can be ascribed to cardiovascular causes, and this number is expected to rise further as the incidence of CVD in the developing world increases as a result of lifestyle changes.
 - A. **Morbidity and mortality.** CVD is the number one killer in the United States, accounting for 36% of all deaths. CVD is responsible for one death every 36 seconds and claims more lives each year than cancer, accidents, chronic obstructive pulmonary disease, and diabetes mellitus combined. One of every five deaths in the United States is caused by coronary heart disease (CHD). There are 15.8 million Americans with a history of myocardial infarction (MI) or angina pectoris. As many as 865,000 Americans have a new MI each year, and 164,000 are victims of sudden cardiac death. The average age at first MI is 65.8 years for men and 70.4 years for women. According to the Centers for Disease Control and Prevention, elimination of all forms of CVD would raise the overall life expectancy by 7 years.
 - B. **Economic consequences of CVD.** The economic burden of CVD and stroke in the United States was estimated to be \$431.8 billion in 2007. In 2004, CVD was the leading cause of hospitalization, contributing to > 6.4 million patient discharges and 4.2 million emergency department visits.
 - C. **Prevention of coronary artery disease (CAD).** Table 43.1 shows important targets for secondary prevention among patients with known coronary or noncoronary vascular disease. The goals for primary prevention are similar, but the cost-effectiveness of medical intervention is not so favorable in all populations. The consequences of modest population-wide risk reduction (e.g., reduction in fat intake [currently 33% of total calories] and cholesterol levels) and lifesaving technologies (e.g., surgery, angioplasty, and coronary care units) have reduced the death rate and possibly contributed to reduced morbidity, but the burden of CVD remains a major challenge.
- II. **HYPERLIPIDEMIA.** Dyslipidemia is an important **correctable predictive factor for CAD**. There is a strong, independent, continuous, and graded relation between total cholesterol (TC) or low-density lipoprotein cholesterol (LDL-C) level and risk of CAD events. This relation has been clearly demonstrated in men and women in all age groups. More than one-half of US adults (105 million) have TC levels > 200 mg/dL, and of these, 37 million have values > 240 mg/dL. In general, a 1% increase in LDL-C level leads to a 2% to 3% increase in risk of CAD.
 - A. **Physiology**
 1. **Lipoproteins** are large molecular compounds that are essential to the transport of cholesterol and triglycerides within the blood. They contain a lipid core composed of triglycerides and cholesterol esters surrounded by phospholipids and specialized proteins known as **apolipoproteins**. The **five major families of lipoproteins** are **chylomicrons, very low density lipoproteins (VLDLs),**

TABLE 43.1 Goals for Secondary Prevention among Patients with Known Vascular Disease

Risk factor	Goal
Hypertension (mm Hg)	140/90 (130/80 if CKD or diabetes)
Dyslipidemia (mg/dL)	LDL < 100 (< 70 in high-risk patients) HDL ≥ 60 Triglycerides < 100
Physical activity	30 min, three or four times per week
Body mass index	≤ 24.9 kg/m ²
Diabetes mellitus	Near-normal blood sugar (HbA1c < 6.5%)
Smoking	Complete cessation

CKD, chronic kidney disease; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

intermediate-density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDLs).

2. **Apolipoproteins** are necessary for the structure and enzymatic processes of lipids. Apolipoprotein A1 (**apo A1**) is a major component of **HDL**, and apolipoprotein B (**apo B**) is the main apolipoprotein for the remaining **non-HDL** lipoproteins.

B. Lipid-lowering trials. Aggressive lipid-lowering drug treatment of persons at various risk levels reduces CAD morbidity and mortality rates and increases overall survival. Although the association between hyperlipidemia and CAD was established much earlier, the demonstration of a relationship between reduction in serum lipid levels and a reduction in all-cause mortality had to await the development of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, or “statins.” Multiple randomized trials have provided overwhelming evidence of the benefit of statins in both primary and secondary prevention of cardiovascular events.

1. **Primary prevention trials**

- a. The **West of Scotland Coronary Prevention Study (WOSCOPS) (1995)** demonstrated that treatment of men at relatively high risk with profoundly elevated cholesterol levels significantly reduced the risk of heart attack and death from heart disease. The double-blind study randomized 6,600 healthy men with a baseline mean LDL-C level of 193 mg/dL to pravastatin (40 mg/d) or to placebo, for an average of 5 years, and demonstrated a 31% relative reduction in the incidence of nonfatal MI or CAD death. Follow-up of this population published in 2007 showed that the statin group continued to experience lower rates of cardiovascular death after a further 10 years, even though only one-third continued to take statins during the additional follow-up period.
- b. The **Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) (1998)** demonstrated benefit among patients with more typical risk profiles, including lower cholesterol values, than among those in the WOSCOPS. AFCAPS/TexCAPS patients had a baseline mean TC level of 220 mg/dL. The study randomized 6,600 patients to lovastatin 20 to 40 mg daily or placebo and demonstrated a 36% relative risk reduction (RRR) for first acute major coronary events in the lovastatin group.
- c. The **Heart Protection Study (HPS) (2002)** randomized 20,536 subjects in a 2 × 2 factorial design to daily simvastatin (40 mg) or placebo and to antioxidants or placebo (the antioxidant arm did not show any benefit or harm).

The study focused on patients who were deemed high risk for CVD but not thought to merit treatment with statins based on the prevalent clinical practice at that time. Increased risk was defined as presence of or history of CAD, cerebrovascular disease, peripheral arterial disease, diabetes mellitus, or treated hypertension. Simvastatin therapy was associated with a 13% reduction in all-cause mortality, including an 18% reduction in coronary death rate. The beneficial impact of statin therapy was seen with respect to all cardiovascular end points, with significant reductions in risk of nonfatal MI, incidence of first stroke, and coronary and noncoronary revascularization. **Treating patients with LDL levels < 100 mg/dL was also associated with a beneficial reduction in vascular events.** The benefit was maintained in patients receiving other cardioprotective medications, such as angiotensin-converting enzyme inhibitors, β -blockers, and aspirin. Although not strictly a primary prevention trial, the HPS provided evidence to support treatment of risk as endorsed by the National Cholesterol Education Program (NCEP) guidelines. However, the HPS results refuted the threshold LDL level (as proposed by NCEP III at that time) below which statins were not previously indicated.

- d. **Pravastatin in Elderly Individuals at Risk of Vascular Disease (PROSPER) (2002)** randomized 5,804 patients between the ages of 70 and 82 years to placebo or pravastatin. These patients had preexisting coronary, cerebral, or peripheral vascular disease or had a history of smoking, hypertension, or diabetes. The study demonstrated a 15% reduction in the composite of coronary death, nonfatal MI, and stroke over a period of 3 years. The study demonstrated efficacy of primary and secondary prevention in the elderly.
- e. The **Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT-LLT) (2002)** randomized 10,355 hypertensive patients with one other coronary risk factor and a baseline mean LDL-C level of 148 mg/dL to pravastatin 20 to 40 mg/d or usual care. The study did not demonstrate a mortality difference in the two arms after a follow-up period of 4.8 years. This lack of observable difference in outcome might have resulted from the relatively modest LDL reduction (17% with pravastatin vs. 8% in usual care) or the fact that 26% of the patients in the “usual care” group were taking a statin at the end of the trial.
- f. The **Anglo-Scandinavian Cardiac Outcomes Trial—Lipid-Lowering Arm (ASCOT-LLA) (2003)** randomized 10,305 patients with hypertension and at least three other cardiovascular risk factors and a baseline mean LDL-C level of 133 mg/dL to atorvastatin 10 mg/d or placebo. The study was stopped prematurely after a median follow-up of 3.3 years by the safety monitoring committee because of a significantly higher incidence of the primary end point (nonfatal MI or fatal CHD) in the placebo group. The study demonstrated a 36% RRR for the primary end point in the atorvastatin group compared with the placebo group. Further analysis demonstrated that the benefit of statin therapy started after only 1 year of treatment. There was also a significant reduction (RRR of 27%) in the incidence of fatal and nonfatal stroke in the atorvastatin group. This study, like the HPS, provided further evidence of the benefit of statins in patients at high risk for CVD without regard for baseline TC or LDL levels.
- g. The **Collaborative Atorvastatin Diabetes Study (CARDS) (2004)** randomized 2,838 diabetic patients with one additional cardiovascular risk factor, no history of CVD, and an average baseline LDL-C of only 117 mg/dL to atorvastatin 10 mg/d or placebo. This study was also terminated prematurely owing to an excess incidence of the primary end point (a composite of acute coronary events, coronary revascularization, or stroke) in the placebo group after a median follow-up of 3.9 years. Overall, the atorvastatin group

had an RRR of 37% for the primary end point and 27% for all-cause mortality. The importance of this trial was its demonstration of the clinical benefit of statin use in diabetic patients regardless of baseline LDL-C level, making a compelling case for statin use in all diabetic patients with at least one additional cardiovascular risk factor. According to the NHANES III data, 82% of diabetic patients in the United States would meet the entry criteria for the CARDS trial.

- h. The **Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) (2005)** trial focused on the prevention of CHD in patients with type 2 diabetes using fenofibrates. The study randomized patients with type 2 diabetes diagnosed after 35 years of age with no clear indication for cholesterol-lowering therapy at baseline to fenofibrate (200 mg/d) or placebo. The study failed to show a difference in the primary composite end point of CHD or nonfatal MI between the two groups at 5-year follow-up. However, several secondary end points were lower in the fenofibrate group including nonfatal MI and coronary revascularization.
- i. The **Japan EPA Lipid Intervention Study (JELIS) (2007)**. The goal of this trial was to evaluate treatment with the fish oil supplement eicosapentaenoic acid (EPA) in addition to statin therapy compared with statin therapy alone among patients with hypercholesterolemia. The study randomized patients in an open-label manner to treatment with EPA (1,800 mg/d) in addition to statin therapy (pravastatin 10 mg/d) or simvastatin (5 mg/d) or to statin therapy alone. At a mean follow-up of 4.6 years, there was a significant reduction in the primary end point of major adverse cardiovascular events in the EPA plus statin group (2.8% vs. 3.5%). This was driven primarily by a significant reduction in rates of unstable angina and a trend toward lower rates of nonfatal MI and revascularization. No difference was seen in sudden cardiac death or fatal MI.
- j. The **Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) (2008)** trial focused on patients with normal LDL-C levels but increased levels of high-sensitivity C-reactive protein (CRP). This was the first clinical trial to demonstrate that statin therapy may benefit patients with low-to-normal LDL levels and no known CVD. The study randomized 17,802 healthy subjects with an LDL-C < 130 mg/dL and a CRP \geq 2.0 mg/L to daily rosuvastatin of 20 mg or placebo. The trial was stopped early for a mortality benefit after a median follow-up of 1.9 years. The study demonstrated that after 1 year of therapy, there were lower levels of LDL-C (55 vs. 110 mg/dL) and lower levels of CRP (2.2 vs. 3.5 mg/L) in the rosuvastatin-treated group. There was also a lower incidence of the primary end point of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization procedure, or confirmed death from cardiovascular cause (0.77 vs. 1.36 events per 100 person-life years) as well as the risk of all-cause mortality (1.00 vs. 1.25 deaths per 100 person-life years) in the rosuvastatin-treated group.
- k. The **Action to Control Cardiovascular Risk in Diabetes Lipid Trial (ACCORD Lipid) (2010)** was designed to evaluate whether the addition of fenofibrate to statin therapy among patients with type 2 diabetes would be effective in preventing cardiovascular events. The study randomized half of the patients within the initial ACCORD trial with type 2 diabetes and treated with a statin medication to fenofibrate (160 mg daily) or placebo. Although a significant reduction in triglyceride level (186 to 170 mg/dL) was seen with the addition of fenofibrate to statin therapy, there was no reduction in the primary end point (first occurrence of cardiovascular death, nonfatal MI, or nonfatal stroke) when compared with statin therapy alone.

In a subgroup analysis, a trend toward benefit of fenofibrate was shown in the group of patients with diabetes that had a significant dyslipidemia (low HDL and high triglycerides). Additional subgroup analysis showed a trend toward harm in women (but not men) in the fenofibrate group that warrants further investigation in future studies.

2. Secondary prevention trials

- a. The **Scandinavian Simvastatin Survival Study (4S) (1994)** was the first secondary prevention trial to demonstrate a clear reduction in total mortality. Simvastatin reduced total mortality among patients with CAD by 30%, largely because of a 42% reduction in deaths from CAD. The 4S treated 4,444 men and women with CAD and mean baseline LDL of 188 mg/dL, with a range of 130 to 266 mg/dL.
- b. The randomized, controlled **Cholesterol and Recurrent Events Trial (CARE) (1996)** was designed to evaluate the effects of treatment with pravastatin on 4,159 persons who had experienced acute MI 3 to 20 months before randomization and had moderately elevated TC levels (mean 209 mg/dL). The benefits of pravastatin therapy in preventing recurrent coronary events were similar in the subset analysis of age, sex, ejection fraction, hypertension, diabetes mellitus, and smoking.
- c. The **Long-Term Intervention with Pravastatin in Ischemic Disease Study (LIPID) (1998)** was the first to examine the use of a statin for patients with a history of unstable angina. The LIPID study provided new data on non-coronary mortality (i.e., stroke) and on other groups, such as women and patients with diabetes, who previously had been underrepresented in clinical trials. LIPID demonstrated improved CAD outcomes among all patients, including those with unstable angina.
- d. The **Veterans Affairs High-Density Lipoprotein Intervention Trial (VA-HIT) (1999)** was a multicenter study that randomized patients with known CHD and low high-density lipoprotein cholesterol (HDL-C) (≤ 40 mg/dL) and LDL-C (≤ 140 mg/dL) levels to gemfibrozil (1,200 mg/d) or placebo with a mean follow-up of 5.1 years. The study showed that gemfibrozil therapy was associated with a significant 22% reduction in the combined incidence of nonfatal MI and CHD death. This was the first lipid intervention trial to show that raising HDL-C concentrations in patients with CHD and low HDL-C and LDL-C levels will reduce the incidence of major coronary events.
- e. **Myocardial Ischemia Reduction with Acute Cholesterol Lowering Trial (MIRACL) (2001)**. This trial demonstrated cardiovascular benefits with initiation of early statin therapy following acute coronary syndrome (ACS). The trial randomized 3,086 adults with unstable angina or non-Q-wave MI to high-dose atorvastatin (80 mg/d) or placebo between 24 and 96 hours after hospital admission. There was a reduction in the primary end point of nonfatal infarction, cardiac arrest with resuscitation, or recurrent symptomatic ischemia requiring hospitalization in the atorvastatin group (14.8% vs. 17.4%, RRR of 16%). The benefit was driven primarily by a 26% reduction in recurrent symptomatic ischemia. The trial did not show a mortality benefit (death, MI, or need for revascularization).
- f. **Pravastatin or Atorvastatin Evaluation and Infection Therapy-TIMI 22 (PROVE-IT-TIMI-22) (2004)**. This trial was designed to determine whether intensive lipid-lowering therapy in patients with ACS reduced major coronary events and mortality more than “standard” lipid lowering. A total of 4,162 patients who had been hospitalized for ACS within the preceding 10 days were randomized to atorvastatin 80 mg/d or pravastatin 40 mg/d. After 2 years of follow-up, the composite end point (all-cause mortality, MI,

unstable angina, coronary revascularization, and stroke) was significantly reduced by 16% with atorvastatin compared with pravastatin. High-dose atorvastatin was well tolerated, with no cases of rhabdomyolysis. Of note, the LDL-C level attained on atorvastatin 80 mg/d was 33 mg/dL lower than on pravastatin with a mean of 62 mg/dL. These results suggested that the use of intensive lipid-lowering therapy to achieve very low LDL-C levels was of benefit in a group of patients at high risk for recurrent coronary events.

- g. **A to Z Trial: Phase Z (2004)—Early Intensive vs. a Delayed Conservative Simvastatin Strategy in Patients with Acute Coronary Syndromes (2004).** This trial studied whether early initiation of high-dose statin therapy would lead to a reduction in long-term cardiac events compared with a more conservative, delayed low-dose statin strategy in high-risk patients with ACS. The trial enrolled a total of 4,497 patients with a recent ACS, TC level ≤ 250 mg/dL, and at least one additional risk factor who were randomized to either intensive statin therapy strategy (simvastatin 40 mg for 1 month, followed by 80 mg through 2 years) or a conservative strategy (placebo for 4 months followed by simvastatin 20 mg through 2 years). Although the study showed an early and sustained reduction in LDL in the aggressive strategy arm, it did not show a significant reduction in the primary composite end point of cardiovascular events (cardiovascular death, MI, readmission for ACS, and CVA) or death from any cause compared with a more conservative strategy. There were also more patients who developed creatine kinase (CK) concentrations more than 10 times the upper limit of normal in the aggressive strategy arm (9 vs. 1) and 3 patients who developed rhabdomyolysis while on simvastatin 80 mg.
- h. **The Treating to New Targets (TNT) (2005)** trial sought to demonstrate the benefit of intensive lipid-lowering therapy in patients with stable coronary disease. The trial randomized 10,001 patients with clinically evident CHD and baseline LDL-C levels < 130 mg/dL to atorvastatin 80 mg/d or atorvastatin 10 mg/d. After 4.9 years of follow-up, the group receiving atorvastatin 80 mg/d had a 22% RRR in the primary composite end point of death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke compared with the group receiving atorvastatin 10 mg/d. High-dose atorvastatin was remarkably safe, with a 1.2% incidence in elevation of alanine aminotransferase (ALT)/aspartate aminotransferase (AST) more than three times the upper limit of normal, compared with a 0.2% incidence in the atorvastatin 10 mg group. Rates of myalgias and rhabdomyolysis were similar between the two groups. This study provided compelling evidence that the use of intensive statin therapy to reduce LDL-C to levels below 100 mg/dL had marked clinical benefit in patients with stable CHD.
- i. **The Incremental Decrease in End Points through Aggressive Lipid Lowering (IDEAL) (2005)** trial randomized 8,888 patients with a prior history of acute MI to atorvastatin 80 mg/d or simvastatin 20 mg/d. After 4.8 years of follow-up, there was a nonsignificant difference in the risk of the composite end point of coronary death, acute MI, or cardiac arrest. However, if either stroke or revascularization was added to the primary end point, the results favored the atorvastatin group, and the associated hazard ratios were similar to the results of PROVE-IT and TNT. Despite the published negative result of this trial, it provided complementary evidence for the benefit of intensive LDL lowering in patients at high risk for coronary events.
- j. **The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: Impact on Global Health outcomes (AIM-HIGH) (2011)** was a study that compared treatment of extended-release niacin versus placebo among statin-treated patients with established heart and vascular disease. The study randomized 3,414 patients with

optimally treated LDL-C and low HDL-C with established vascular disease (documented by coronary angiography or by prior MI, or carotid angiography or prior ischemic stroke, or peripheral arterial disease) to extended-release niacin (1,500 to 2,000 mg/d) or placebo. There was no significant difference in the primary composite outcome of CHD death, nonfatal MI, ischemic stroke, hospitalization for ACS, or symptom-driven coronary/cerebral revascularization (16.4% in the extended-release niacin group vs. 16.2% in the placebo group). The study was terminated 18 months early after it was evident that the addition of extended-release niacin would not be beneficial. Furthermore, there was a small (numerical) excess in ischemic strokes and hospitalizations for ACS.

3. Meta-analyses

- a. **CTT Collaborators (*Lancet*, 2005).** A large meta-analysis of 90,056 individuals from 14 randomized trials of statin drugs, this analysis demonstrated an impressive 12% reduction in all-cause mortality for each 1 mmol/L (39 mg/dL) reduction in LDL. There was a 19% reduction in coronary mortality and 21% reduction in MI, coronary revascularization, and stroke. Statin use showed benefit within the first year of use, but was greater in subsequent years. Statins were also remarkably safe, with no increase in cancer seen and a 5-year excess risk of rhabdomyolysis of 0.1%.
 - b. **Cannon—Intensive Statin Therapy (*J Am Coll Cardiol*, 2006).** A meta-analysis of 27,548 patients from four trials that investigated intensive versus standard lipid-lowering therapy found a significant 16% odds ratio reduction in coronary death or MI in the group that received intensive therapy. There was a nonsignificant trend toward decreased cardiovascular mortality.
- C. Management of lipids.** Despite overwhelming evidence supporting the treatment of dyslipidemia, a large number of patients remain untreated. The NCEP Adult Treatment Panel III (ATP III) has released guidelines for the treatment of hyperlipidemia in adults. These guidelines focus on identification of the risk of cardiovascular morbidity and appropriate targeting of therapy. The guidelines were last updated in 2004, with the next update planned for 2012.

1. Guidelines for primary prevention of CAD events based on the NCEP ATP III

- a. **TC, LDL-C, and HDL-C levels.** All adults 20 years or older and **without a history of CAD or other atherosclerotic disease** should have a fasting lipid panel (i.e., TC, LDL-C, HDL-C, and triglyceride levels) every 5 years. If a non-fasting lipid panel is obtained and the TC level is 200 mg/dL or the HDL-C is < 40 mg/dL, a follow-up fasting lipid panel is recommended (Table 43.2).
- b. **Determination of risk.** The patient's risk of future events is based on the presence of known CAD or clinical atherosclerosis in a noncoronary bed, diabetes mellitus (i.e., CAD equivalent), and other risk factors. These include age (men 45 years or older and women 55 years or older), smoking, hypertension (> 140/90 mm Hg or use of antihypertensive medication), family history of premature CAD (defined as CAD in first-degree male relatives before the age of 55 years and in a first-degree female relative before the age of 65 years), and low HDL-C (< 40 mg/dL). An **HDL-C level 60 mg/dL or greater is considered a negative risk factor**. Patients are classified into three categories of risk based on these factors.
 - (1) **CHD risk.** Patients with highest risk of cardiovascular events are those with established CAD or evidence of atherosclerosis in noncoronary beds (i.e., abdominal aortic aneurysms, peripheral arterial disease, or symptomatic carotid disease), **diabetes mellitus**, or presence of multiple risk factors conferring a calculated 10-year risk of > 20%. The risk is calculated according to the Framingham risk score. The target LDL-C level for this group is < 100 mg/dL.

TABLE 43.2 Lipid Classification According to the National Cholesterol Education Program III

Risk factor	Goal
LDL-C	
< 100	Optimal
100–129	Near or above optimal
130–159	Borderline high
160–189	High
≥ 190	Very high
Total cholesterol	
< 200	Desirable
200–239	Borderline high
≥ 240	High
HDL-C	
< 40	Low
≥ 60	High

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

- (2) The second category includes patients with multiple risk factors and an estimated 10-year risk of adverse events between 10% and 20%. The target LDL-C level for this group is < 130 mg/dL.
 - (3) The third category includes those with no or one risk factor and an estimated 10-year risk of < 10%. The target LDL-C level in this group is < 160 mg/dL.
- c. **Treatment of dyslipidemia. The treatment of hyperlipidemia requires two approaches: therapeutic lifestyle changes (TLCs) and medications** (Table 43.3). To achieve target LDL levels, most patients need both approaches simultaneously.
- (1) **CHD risk equivalent.** These patients are at the highest risk of adverse events and, therefore, benefit the most from aggressive treatment. NCEP III, whose recommendations were published in 2001, had recommended therapy with a statin and TLCs if the LDL-C level was 130 mg/dL or greater. In patients with LDL-C levels between 100 and 130 mg/dL, it is suggested that the clinician use judgment as to whether to begin treatment with a statin, TLCs, or another agent such as niacin or a fibrate. **The 2004 update, however, was more definitive and recommended starting a statin and TLCs for all patients with a CHD risk equivalent with LDL-C levels 100 to 130 mg/dL.** This was based on cited evidence from the HPS and was further supported by the CARDS and ASCOT-LLA trials. In patients who have a baseline LDL-C concentration of < 100 mg/dL, the 2004 update stopped short of recommending initial use of a statin, but acknowledged that there was evidence for statin use in this group regardless of the LDL-C level. It did, however, state that initiation of a statin drug in patients with an initial LDL-C < 100 mg/dL who are

TABLE 43.3 Low-Density Lipoprotein Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes and Drug Therapy in Different Risk Categories

Risk category	LDL goal (mg/dL)	LDL level at which to initiate TLC (mg/dL)	LDL level at which to consider drug therapy
CHD or CHD risk equivalent (10-y risk > 20%)	< 100	≥ 100	≥ 130 mg/dL (100–129 mg/dL: drug optional)
2+ risk factors (10-y risk ≤ 20%)	< 130	≥ 130	10-y risk 10–20%: ≥ 130 mg/dL 10-y risk < 10%: ≥ 160 mg/dL
0–1 risk factor	< 160	≥ 160	≥ 190 mg/dL (160–189 mg/dL: LDL-lowering drug optional)

CHD, coronary heart disease; LDL, low-density lipoprotein; TLC, therapeutic lifestyle changes.

at “very high risk” for future CVD events, with the goal of lowering the LDL-C to < 70 mg/dL, was a “reasonable therapeutic option.” The cited evidence included the HPS and PROVE-IT–TIMI-22 trials. The publication of the TNT trial provided even more evidence for intensive lipid lowering in all patients with clinically evident CHD. **Given the balance of evidence in the most recently published trials and meta-analyses, a reasonable current approach for most clinicians would be to initiate statin therapy in all patients with CHD or a CHD risk equivalent, regardless of baseline LDL-C level, with a goal LDL-C of ≤ 70 mg/dL for patients with CHD or at high risk for future CVD events.**

- (2) **Ten-year risk of 10% to 20%.** These are generally patients with two or more risk factors for CVD events. The target LDL-C level for this group is < 130 mg/dL. The 2004 ATP III update stated that an LDL-C goal < 100 mg/dL is a therapeutic option, and initiation of statin therapy along with TLCs for patients with baseline LDL-C level 100 to 130 mg/dL was reasonable. This recommendation was based on evidence from the HPS and ASCOT-LLA trials.

- (3) **Ten-year risk < 10% and zero or one risk factor.** These patients should be treated with TLC to achieve a target LDL-C level < 160 mg/dL. If the LDL-C concentration remains above 160 mg/dL after 3 months of TLCs, drug therapy may be considered. Pharmacotherapy is recommended in those with LDL-C levels > 190 mg/dL. Factors favoring the use of drugs include a 10-year risk close to 10% or the presence of a severe risk factor such as a strong family history of premature CAD, a very low HDL level, poorly controlled hypertension, or heavy smoking.

2. Types of therapy

- a. TLCs encompass **increased physical activity, ideal weight maintenance, and a diet** that includes a reduced intake of saturated fat (< 7% of total calories) and cholesterol (< 200 mg/d). Other TLCs are listed in Table 43.4. Intake of *trans*-fatty acids should be kept to a minimum. For most patients, it is essential to reduce saturated fat intake over total fat intake; for patients with metabolic syndrome, a fat intake of 30% to 35% may be optimal for reducing lipid and nonlipid risk factors. High-carbohydrate diets may worsen the lipid abnormalities in these patients. Dietary carbohydrates should be

TABLE 43.4 Components of Therapeutic Lifestyle

Component	Recommendation	Approximate LDL reduction
Diet		
Saturated fat	< 7% of total calories	8–10%
Dietary cholesterol	< 200 mg/d	3–5%
Polyunsaturated fat	Up to 10% of total calories	
Monounsaturated fat	Up to 20% of total calories	
Total fat	25–35% of total calories	
Carbohydrate	50–60% of total calories	
Dietary fiber	20–30 g/d	
Total protein	15% of total calories	
Therapeutic options for LDL lowering		
Plant stanols/sterols	2 g/d	6–15%
Increased viscous soluble fiber	5–10 g/d (consumption of 10–25 g/d may have added benefit)	3–5%
Physical activity	Enough moderate activity to expend at least 200 kcal/d	

LDL, low-density lipoprotein.

derived predominantly from foods rich in complex carbohydrates, such as whole grains, fruits, and vegetables. Daily intake of 5 to 10 g of viscous fiber reduces LDL levels by approximately 5% and the use of plant stanols and sterols (2 to 3 g/d) by another 6% to 15%. **TLCs can achieve an almost 30% reduction in LDL-C level in highly motivated individuals and should form the cornerstone of all preventive activity.** Benefits of LDL-C lowering may be evident within 6 to 12 months, although the individual response to a cholesterol-lowering diet depends on many factors. Some of the response is genetically determined, and increased body mass index is associated with less response to dietary change. LDL-C should be measured 6 weeks after initiating TLC diet, and if the goals are not met, intensification of TLCs and use of plant sterols or stanols should be considered. Referral to a dietitian for education and dietary counseling is often invaluable at this stage. If, after 3 months of TLCs, adequate control is not achieved, drug therapy should be considered.

- b. **Pharmacotherapy.** The high efficacy of statins in lowering LDL-C level and their demonstrated mortality benefits make them the agents of first choice for treatment of most forms of hyperlipidemia. Table 43.5 summarizes the most commonly used agents affecting lipoprotein metabolism.

- (1) **HMG-CoA reductase inhibitors.** The third report of the NCEP ATP included **HMG-CoA reductase inhibitors** among the first-line alternatives in the management of hypercholesterolemia. The category includes six drugs: lovastatin, simvastatin, pravastatin, fluvastatin, atorvastatin, and rosuvastatin.

TABLE 43.5 Drugs Affecting Lipoprotein Metabolism

Drug class	Agents and daily doses	Lipid/lipoprotein effects	Side effects	Contraindications
HMG-CoA reductase inhibitors (statins)	Lovastatin (20–80 mg) Pravastatin (20–40 mg) Simvastatin (20–80 mg) Fluvastatin (20–80 mg) Atorvastatin (10–80 mg) Rosuvastatin (10–40 mg)	LDL-C ↓ 18–55% HDL-C ↑ 5–15% TG ↓ 7–30%	Gastrointestinal distress Myopathy Increased liver enzymes	Absolute: – Active or chronic liver disease Relative: – Concomitant use of certain drugs ^a
Bile acid sequestrants	Cholestyramine (4–16 g) Colestipol (5–20 g) Colestesvelam (2.6–3.8 g)	LDL-C ↓ 15–30% HDL-C ↑ 3–5% TG—no change or increase	Gastrointestinal distress Constipation Decreased absorption of other drugs	Absolute: – Dysbeta-lipoproteinemia – TG > 400 mg/dL Relative: – TG > 200 mg/dL
Nicotinic acid	Immediate release (crystalline nicotinic acid [1.5–3 g]) Extended release (Niaspan; 1–2 g) Sustained release (1–2 g)	LDL-C ↓ 5–25% HDL-C ↑ 15–35% TG ↓ 20–50%	Flushing Hyperglycemia Hyperuricemia (or gout) Upper GI distress Hepatotoxicity	Absolute: – Chronic liver disease – Severe gout Relative: – Diabetes – Hyperuricemia – Peptic ulcer disease
Fibric acids	Gemfibrozil (600 mg bid) Fenofibrate (200 mg) Clofibrate (1,000 mg bid)	LDL-C ↓ 5–20% (may be increased in patients with high TG) HDL-C ↑ 10–20% TG ↓ 20–50%	Dyspepsia Gallstones Myopathy	Absolute: – Severe renal disease – Severe hepatic disease

^aCyclosporine, macrolide antibiotics, various antifungal agents, and cytochrome P450 inhibitors (fibrates and niacin should be used with appropriate caution).

GI, gastrointestinal; HDL-C, high-density lipoprotein cholesterol; HMG-CoA, 3-hydroxy-3-methylglutaryl coenzyme A; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride.

- (a) **Effectiveness.** When dietary measures are inadequate, HMG-CoA reductase inhibitors effectively **lower TC and LDL-C levels in patients with mixed hyperlipidemias** (i.e., elevated cholesterol and triglyceride levels). HMG-CoA reductase inhibitors are **extremely effective in reducing LDL-C levels in most patients with primary hypercholesterolemia**. HMG-CoA reductase inhibitors decrease TC by 15% to 60% and LDL-C by 18% to 55% and increase HDL-C levels by 5% to 15%. Declines in apo B levels commensurate with reductions in LDL have been demonstrated. Statins also reduce triglyceride levels by 7% to 30% but have minimal effects on apo A1, apo A2, and lipoprotein (a) [Lp(a)]. **All statin drugs at the starting dose and within one to two dose titrations are well tolerated, efficacious,** and reasonably equivalent with respect to safety profiles.
- (b) **Adverse effects.** Statins are remarkably safe drugs, with a low incidence of side effects. However, they are contraindicated in pregnancy.
- (i) **Minor side effects.** The most common side effects are **mild gastrointestinal disturbances** (e.g., nausea, abdominal pain, diarrhea, constipation, and flatulence). Headache, fatigue, pruritus, and myalgias are other minor side effects, but none of these complaints usually warrant discontinuation of therapy.
- (ii) **Liver function test abnormalities.** Mild, transient elevations in liver enzymes have been reported with all HMG-CoA reductase inhibitors. Marked elevation of transaminases is rare, but clinicians should avoid or use caution before starting statins in patients with acute or chronic liver disease. In the HPS, only 0.5% of patients had to stop treatment because of elevated ALT levels. Even when taking the highest dose of atorvastatin (80 mg), patients in PROVE-IT and TNT had only a 3.3% and 1.1% incidence, respectively, of transaminase elevation more than three times the upper limit of normal. In general, for each doubling of a statin dose, there is a 0.6% increase in risk of elevation of transaminase levels. **Current recommendations state that therapy should be discontinued when greater than threefold elevation occurs.** Enzyme levels typically return to normal within 2 weeks. Lower doses of the same medication can be reinstituted or a different statin can be tried. **Monitoring of hepatic aminotransferase levels is recommended for those taking HMG-CoA reductase inhibitors, but the frequency of monitoring has been debated.** Current package inserts for most statins recommend obtaining a liver panel prior to initiation of statin therapy, prior to dose titration, and when “clinically indicated.” More frequent monitoring is recommended for patients taking the highest dose of a statin. In recent clinical trials, the high-dose statin that appears to have the highest incidence of transaminase elevation is atorvastatin. A panel of hepatologists who examined the potential hepatotoxicity of statins made a recommendation to obtain a liver panel prior to initiating statins as a baseline measurement of hepatic transaminases and bilirubin. If the baseline measurements were within normal limits, the panel recommended follow-up measurement of transaminases only if there was symptomatic or physical evidence of liver disease. An ACC/AHA/NHLBI clinical advisory panel on the safety and use of statins recommends measurement of transaminases at baseline, 12 weeks after starting therapy, and then annually or more frequently if indicated.

- (iii) **Myopathy**, a rare but potentially serious side effect of HMG-CoA reductase inhibitors, presents with muscle pain, stiffness, or aching and elevations in serum CK level to more than 10 times the upper limit of normal. **CK measurements are not needed unless symptoms occur.** Statin-naïve patients should be warned to report symptoms of muscle pain or stiffness immediately if they occur after starting the drug. The risk of myopathy may be increased in the elderly, those with a low body mass index, those with multisystem disease such as chronic renal failure, those in the perioperative period, and those on multiple medications. Simvastatin 80 mg has been associated with a slightly higher incidence of myopathy and rhabdomyolysis compared with other statins, especially when combined with gemfibrozil. This could be due to the decreased rate of plasma clearance of simvastatin in older versus younger patients. Death from statin-induced rhabdomyolysis is exceedingly rare, with an incidence of 1.5 deaths per 10 million prescriptions. Statin-associated myalgias (muscle symptoms without elevations in serum CK) occur with somewhat higher frequency, about 1.4% to 1.5% in published clinical trials, and can appear at any time during statin therapy, even years after initiation of treatment. Muscle symptoms usually resolve with discontinuation of the statin. There is recent evidence that statin inhibition of mitochondrial coenzyme Q10 may be responsible for statin-induced myalgias, and there is evidence from small clinical trials that oral coenzyme Q10 supplementation may decrease symptoms of statin-associated myalgias.
- (iv) **Drug interactions.** When statins are used in combination with certain pharmaceutical agents, such as erythromycin, gemfibrozil, azole antifungals, cimetidine, methotrexate, or cyclosporine, the risks of CK elevation and myositis increase. These drug combinations should be avoided or used judiciously with interval measurements of CK levels and liver function. Pravastatin and fluvastatin are safer in combination with other drugs because these two drugs do not use the cytochrome P450 3A4 microsomal pathways for metabolism. Verapamil and amiodarone are two commonly used cardiovascular agents that inhibit this pathway, and the concurrent use of simvastatin, atorvastatin, or lovastatin may, therefore, predispose to an increased risk of myositis. Recently, the US Food and Drug Administration (FDA) has recommended that simvastatin should not be prescribed at a dose of 80 mg, given the higher rate of myopathy at this dose unless patients have already safely taken this dose for > 12 months. Patients requiring this dose to maintain lipid goals should be transferred to another statin drug capable of achieving that goal. Simvastatin dosage in combination with amiodarone, diltiazem, or verapamil should not exceed 10 mg daily and should not exceed 20 mg daily in combination with amlodipine or ranolazine.
- (2) **Bile acid sequestrants** lower LDL-C level by interfering with reabsorption of bile acids in the distal ileum, reducing the amount returned to the liver. They are safe and free of systemic side effects because they are not systemically absorbed; however, gastrointestinal side effects such as constipation are common, and compliance is poor as a result. The average LDL level decrease is approximately 15% to 30%, with a small rise seen in HDL level (3% to 5%). Triglycerides show no change or may

rise; therefore, these agents should be avoided in patients with elevated triglycerides. Two small angiographic trials, the NHLBI Type II Coronary Interventional Study and the St. Thomas Atherosclerosis Regression Study (STARS), have demonstrated reduced progression of CAD on serial angiograms in men with hypercholesterolemia who were taking cholestyramine. These agents may be of particular benefit in patients with minor elevation in LDL-C, for young patients, for women considering pregnancy, and in combination with a statin in those with very high LDL-C levels. In a pregnant patient, additional supplementation of iron and folate may be necessary because resins used over the long term can interfere with their absorption.

- (3) **Nicotinic acid or niacin.** Niacin affects all lipid parameters favorably (i.e., LDL reduction of 5% to 25%, triglyceride reduction of 20% to 50%, and HDL elevation of 15% to 35%). It is one of the only agents that reduces Lp(a) significantly (up to 30%). Unfortunately, compliance is poor because of frequent side effects. Flushing and pruritus, gastrointestinal discomfort, glucose intolerance, and hyperuricemia often accompany the use of niacin. Hepatotoxicity is rare but is more commonly seen with the sustained-release preparation. It is often heralded by a dramatic reduction in lipid levels. There are limited data on long-term therapy with this agent. Niacin may be particularly useful for patients who do not have substantial elevations in their LDL-C levels, and low doses may be used to treat diabetic dyslipidemia. High doses should be avoided in patients with diabetes, and the drug should be avoided in those with a history of gout, peptic ulcer disease, or active hepatic disease.
- (4) **Fibrates are effective at lowering triglyceride levels** by 20% to 50% and raising HDL levels by 10% to 20%. The mechanism of action involves activation of the nuclear transcription factor peroxisome proliferator-activated receptor alpha, with resultant increases in hepatic synthesis of apo A1 and A2 (raising HDL) and increase in lipoprotein lipase-mediated lipolysis, thus lowering triglyceride levels. LDL level reduction varies with the agent used and may range from 5% to 20% in patients who are not hypertriglyceridemic. Fenofibrate appears to lower LDL more effectively than gemfibrozil. Although a higher mortality rate was seen in the clofibrate arm of the World Health Organization (WHO) clofibrate study, such a finding was not seen in subsequent studies of gemfibrozil or fenofibrate. These agents have been demonstrated to impart a reduction in risk of CAD events and are of use in patients with elevated triglycerides. The VA-HIT (1999) found a reduction in fatal and nonfatal MI with gemfibrozil use in men with CAD who had low HDL levels (mean of 32 mg/dL), but the FIELD trial (2005) did not find a significant reduction in the primary end point of CAD death or MI in diabetic patients. Although fibrates are often used in combination with statin therapy to treat mixed dyslipidemia, there are no studies demonstrating reduction in clinical events with this approach. This combination increases the risk of myopathy. For patients with very high triglyceride levels (> 1000 mg/dL), fibrate therapy reduces the risk of pancreatitis.
- (5) **Cholesterol absorption inhibitors** such as ezetimibe inhibit cholesterol absorption by the enterocyte. Ezetimibe reduces cholesterol absorption from the small bowel by 23% to 50% and reduces serum LDL level by 14% to 20% when used in combination with a statin. Reduction in clinical end points or surrogate end points has not been demonstrated for this group of drugs in all people. The SHARP trial (Study of Heart and Renal Protection) reported that cholesterol lowering with a combination

of simvastatin and ezetimibe in patients with chronic kidney disease significantly reduced the risk of major atherosclerotic events by 17%, including significant reductions in the risk of nonhemorrhagic stroke and revascularizations, when compared with placebo. However, the ENHANCE study failed to demonstrate any additional benefit of the use of ezetimibe added to statin over statin alone in slowing progression of carotid intimal thickness in a cohort of patients with familial hyperlipidemia. A number of large-scale studies are currently in progress seeking to determine the utility of a statin ezetimibe combination on hard cardiovascular end points. IMPROVE-IT, a phase III trial comparing ezetimibe/simvastatin versus simvastatin in subjects with stabilized high-risk ACS, is currently underway.

- (6) **Cholesteryl ester transfer protein (CETP) inhibitors** such as torcetrapib, dalcetrapib, anacetrapib, and evacetrapib inhibit the process in which triglycerides from VLDL or LDL are exchanged for cholesteryl esters from HDL, resulting in higher HDL levels and reduction of LDL levels. Results from a torcetrapib study in 2004 demonstrated a significant increase in HDL (61%) and a decrease in LDL (17%) when receiving the drug in addition to atorvastatin and a 46% increase in HDL when receiving the drug alone. However, the phase 3 ILLUMINATE trial was terminated in 2006 after an increase of cardiovascular events and mortality was shown to be associated with the drug. Early results from the DEFINE trial (Determining the Efficacy and Tolerability of CETP Inhibition with Anacetrapib) have reported a decrease of LDL by 36% and increase of HDL by 138% without associated increased CVD death or events. This is a medium-sized safety trial with 2-year follow-up due to complete in December of 2012.

- (a) **Choice of an agent and combination therapy.** The use of statin therapy for treatment of hyperlipidemia should be guided by the expected change in LDL-C levels (Table 43.6). Most statins have a log-linear dose-response pattern, with each doubling of dose associated with a further 7% reduction in LDL-C levels. Adverse effects of statins are also dose dependent and rise with the use of higher doses.

- (i) **HMG-CoA reductase inhibitors and bile acid resins.** In isolated forms of LDL elevation, this combination exhibits highly complementary mechanisms of action. The combination of a statin with a bile acid sequestrant is ideal, owing to the lack of

TABLE 43.6 Average Reduction in Low-Density Lipoprotein Cholesterol Associated with the Starting Dose of Statin Agents

Agent	Average LDL-C reduction (%)
Lovastatin (20 mg)	24
Pravastatin (20 mg)	24
Simvastatin (20 mg)	35
Fluvastatin (20 mg)	18
Atorvastatin (10 mg)	37
Rosuvastatin (10 mg)	47

LDL-C, low-density lipoprotein cholesterol.

potentiation of side effects. The sequestrant provides little added toxicity, and the LDL-C lowering needed may not necessitate a full sequestrant dosage. Unfortunately, patient compliance with the combination is poor because of the common side effects of resins. Although the combination may reduce **LDL level by as much as 70% in some patients**, there appears to be a ceiling effect, with no LDL lowering occurring beyond the original level with an increase in dose of either agent.

- (ii) **Combining a statin with niacin** is attractive because it can favorably influence all lipid subfractions. The side effects of the combination are increased but not synergistic, and the risk of myopathy may be lower than previously believed. The main serious side effect of the combination is hepatotoxicity, which may be reduced by using extended-release niacin. In small studies using this combination, the risk of hepatotoxicity (i.e., persistent elevation of AST or ALT of more than three times the upper limit of normal) at niacin doses of 2 g/d was about 1%.
- (iii) The combination of a statin plus fibrates is highly effective for treating mixed hyperlipidemias. Although theoretically appealing, no reduction in clinical events has been demonstrated with this approach. The combination is associated with an increased risk of myopathy. Although earlier work suggested a higher incidence, later studies suggest this complication may be seen in approximately 1% of patients with the currently used agents.
- (iv) The combination of a statin plus ezetimibe has been studied in small trials and has proved to be highly safe and effective at lowering LDL-C levels. Given the small number of patients treated and short follow-up periods, it is suggested that this combination should be reserved for the patients who fail maximal statin doses or are intolerant of statins.

3. Therapy of specific lipid disorders

- a. Very high LDL levels usually result from inherited disorders of lipoprotein metabolism and carry a high risk of premature atherosclerosis with its attendant morbidity and mortality. **Hypothyroidism** may be associated with markedly elevated LDL levels and should be ruled out in any patient presenting with elevated LDL level. Most of these patients respond to high-dose statin therapy in addition to dietary restrictions. The addition of a bile acid sequestrant with an additional third agent (i.e., niacin) is often warranted to achieve target levels. Ezetimibe is another agent that may prove useful in this group. Therapy should be initiated early, and family members should be screened for hyperlipidemia. Patients with homozygous familial hyperlipidemia are deficient in LDL receptors, and measures that reduce cholesterol absorption (e.g., diet, ileal exclusion, bile acid sequestrants, and ezetimibe) or act by LDL receptor upregulation (e.g., statins) are largely ineffective. These patients are treated with LDL apheresis and should be managed in tertiary care centers only.
- b. **Elevated triglyceride levels** may be caused by many factors, and more than one cause may be active in a given patient. **Minor elevations in triglyceride levels (150 to 299 mg/dL)** are usually caused by obesity, sedentary lifestyle, smoking, excess alcohol intake, and high-carbohydrate diets. In other patients, secondary causes such as diabetes, renal failure, Cushing's disease, nephrotic syndrome, or medications (e.g., protease inhibitors, corticosteroids, retinoids, and oral estrogens) may be responsible. Genetic causes may be pertinent to others. The therapy for this group of patients involves

identification and treatment of secondary causes (if present), change in medications, and lifestyle changes. These patients benefit from total caloric restriction and switching from a very high carbohydrate diet to a more balanced diet. Very high **triglyceride levels (≥ 500 mg/dL)** usually result from genetic defects of lipoprotein metabolism; in some patients, there is a combination of factors at play. These patients are at risk for acute pancreatitis (especially with triglyceride levels $> 1,000$ mg/dL), and treatment is directed at prevention of this condition. This is achieved with a combination of dietary measures (using very low fat diets [$< 15\%$ calories from fat] and substituting medium-chain fatty acids in patients with triglyceride levels $> 1,000$ mg/dL), increasing physical activity, maintaining optimal weight, and initiating fibrates or niacin therapy. Fibrates are especially efficacious in this group. Statins are not especially effective agents for triglyceride reduction and should be considered only after the other two agents. Patients with an **intermediate rise in triglyceride levels (200 to 499 mg/dL)** are a more heterogeneous group, with a wide array of underlying pathogenetic mechanisms at play. This pattern is often a result of an intersection of poor lifestyle, secondary causes, and genetic factors. These patients often have other markers of increased atherogenic risk, such as increased small LDL, low HDL, or elevated VLDL remnants. They need to be treated aggressively to bring the LDL level to the target; statins, with their ability to lower non-HDL-C, are the preferred agents. **After the LDL target has been achieved, the secondary goal is non-HDL-C (goal of 30 mg/dL higher than target LDL-C).** These patients also need aggressive TLCs. High-dose statins often suffice to achieve the LDL-C and non-HDL-C goals, but for most patients, a second agent becomes necessary. The choices are niacin or fibrates in addition to a statin; these combinations carry an increased risk of hepatotoxicity or myopathy, and careful monitoring for these is essential. Refractory cases may benefit from fish oil supplements (> 3 g/d), which, by reducing VLDL production, can lower the serum triglyceride concentration by as much as 50% or more; however, many currently available over-the-counter fish oil supplements contain $< 50\%$ active omega-3 fatty acids. The commercial preparation Omacor, which has been available for many years in Europe and is now also available in the United States, contains 90% omega-3 fatty acids. The US FDA limited approval for Omacor to the treatment of severe hypertriglyceridemia (≥ 500 mg/dL) because of concerns that it appears to increase LDL-C levels. Weight loss by obese patients should be encouraged; it is associated with an improvement in the lipid profile and facilitates pharmacologic therapy if still necessary.

- c. **Low HDL-C** levels often accompany minor or modest elevations in triglyceride levels. Low HDL level has been shown in epidemiologic studies to be an independent risk factor of CVD. However, despite a multitude of research on currently available therapies to raise HDL and recent investigation of several newer agents that raise HDL, there has been no conclusive evidence that raising serum HDL-C levels contributes to lower rates of CVD. Current guidelines specify that raising HDL should be a tertiary goal, after LDL and non-HDL-C goals have been reached. In patients who have isolated low HDL levels without any elevation in triglyceride levels, the first goal is to identify and modify lifestyle factors (e.g., high-carbohydrate diet, sedentary lifestyle, obesity, and smoking) and medications (e.g., progestational agents and anabolic steroids). The next step encompasses calculation of 10-year risk and treating LDL-C with a statin when appropriate. The AFCAPS/TexCAPS study found a clear benefit for statin therapy in patients with low HDL-C levels. In patients who continue to have low HDL-C levels despite

lifestyle modifications and who are at goal for LDL and triglycerides, either niacin or fibrate therapy is a reasonable choice to raise HDL-C.

- d. **Diabetic dyslipidemia.** Patients with diabetes are at an increased risk for cardiovascular events and fare poorly after CAD manifests. Diabetes is associated with an increase in small LDL particles and is often associated with high triglyceride and low HDL levels. Hyperglycemia is an independent risk factor for CAD. Primary prevention is important in this group and was demonstrated to be efficacious in the HPS trial. **All diabetic patients (irrespective of LDL-C level) should be considered for statin therapy and TLCs.** Secondary goals include improved non-HDL-C levels and treatment for elevated triglyceride levels. Blood sugar control and insulin therapy often facilitate the former, but fibrates or low-dose niacin may be necessary in some patients. Patients with diabetes also often have coexisting hypertension. Blood pressure control and smoking cessation are essential because both interventions are highly effective at reducing cardiovascular events in this population.

ACKNOWLEDGMENTS: *The authors acknowledge the contributions of Drs. Hintinder S. Gurm, JoAnne Micale Foody, and Matthew Kaminski to previous editions of this chapter.*

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USEFUL INTERNET RESOURCES

Comprehensive Lipid News, Education, and Discussion from Baylor: <http://www.lipidsonline.org/>
 Framingham 10-year risk calculator: <http://hp2010.nhlbi.nih.net/atpui/calculator.asp?usertype=pub>
 NHLBI Guidelines based on NCEP/ATPIII: <http://www.nhlbi.nih.gov/guidelines/cholesterol/atglance.htm>
 NHLBI National Cholesterol Education Program: <http://www.nhlbi.nih.gov/about/ncep/>

Nonlipid Cardiovascular Risk Factors

I. INTRODUCTION. Dyslipidemia constitutes a strong and well-described risk factor for the development of coronary artery disease (CAD). Almost one-half of myocardial infarctions (MIs) in the United States occur in individuals without overt lipid abnormalities. Additional risk factors, including hypertension (HTN), diabetes, obesity, and lifestyle, must be addressed to reduce the incidence of cardiovascular events. This chapter describes these cardiovascular risk factors (except diabetes, which is discussed in Chapter 45). Novel biomarkers and risk factors are also discussed.

II. HYPERTENSION. HTN contributes to all cardiovascular comorbidities: CAD, MIs, cerebrovascular accident (CVA), systolic heart failure, diastolic heart failure, and peripheral vascular disease (PVD). It is associated with increased total mortality among men and women of all ages and ethnic groups, regardless of CAD. It is defined as a blood pressure of $\geq 140/90$ mm Hg **or** the need for antihypertensive medication. It is thought to be present in at least 30% of the US adult population. Evidence from the Framingham Heart Study suggests that this is underestimated, as normotensive 55-year-old persons have a 90% residual lifetime risk of developing HTN.

A. Etiology. HTN is a complex disease modified by environmental and genetic determinants.

1. Genetics. HTN does not follow the classic Mendelian rules of inheritance attributable to a single gene locus.

a. However, Liddle syndrome (mutation of **chimeric 11- β -hydroxylase-aldosterone synthase gene**) and variants in the angiotensinogen locus are documented exceptions that cause primary HTN among whites.

b. Other potential candidate genes include various components of the **renin-angiotensin-aldosterone system, the kallikrein-kinin system, and the sympathetic nervous system.**

2. Increased left ventricular (LV) mass and LV wall thickness and altered peripheral vascular capacity and responsiveness occur more frequently among patients with a family history of HTN.

3. Contributors to HTN include variations in sodium intake, alcohol intake, renal function, vascular function, the sympathetic nervous system, the renin-angiotensin system, hyperinsulinemia/insulin resistance, and prostaglandins.

B. HTN impact on cardiovascular risk and mortality

1. Positive relationship between systolic and diastolic blood pressures and cardiovascular risk has long been recognized.

a. The **Multiple Risk Factor Intervention Trial (MRFIT)**. Prospective study (11.6 years of average follow-up period) with more than 361,000 subjects demonstrated the relationship between blood pressure and CAD. Baseline blood pressure elevations increased risk for CAD. The relationship was

stronger for systolic blood pressure than for diastolic blood pressure. Death rate for men with systolic blood pressures of 140 to 149 (2.4/1,000) and 150 to 159 mm Hg (3.1/1,000) was 40% higher compared with men with a baseline systolic blood pressure < 120 mm Hg.

- b. Death rate at follow-up can be lowered by 36% with primary prevention of HTN in the general population. In addition, rates of stroke and CAD fall with antihypertensive therapy.
- c. Subjects with blood pressure < 120/< 80 mm Hg have the fewest cardiovascular events. The recommended treatment cutpoint is 140/90 mm Hg.
- d. **Prehypertension.** This is defined as blood pressure within the high-normal range (120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic) and which may confer some increased risk for cardiovascular disease. Risk ratios of 2.5 for women and 1.6 for men have been reported in patients in the prehypertensive range. These patients should undertake lifestyle modifications (e.g., diet, exercise, and weight loss) to help prevent or delay the development of frank HTN in the future.
- e. The gradual rise in blood pressure over a person's lifetime and the increased prevalence of **HTN among the elderly** are **not benign**. Epidemiologic studies of the elderly demonstrate a U-shaped relationship between blood pressure and mortality. After adjustment for deaths within the first 3 years of the follow-up period, there is a positive linear relationship between blood pressure, cardiovascular disease mortality, and all-cause mortality. Isolated systolic HTN increases as the population ages, which confers increased risk for morbidity and mortality.
 - (1) **Systolic Hypertension in the Elderly Program (SHEP)** showed that 8% of persons aged 60 to 69 years have isolated systolic HTN, defined as systolic blood pressure > 160 mm Hg and diastolic blood pressure < 90 mm Hg, as do 11% of those aged 70 to 79 years and 22% of those aged 80 years or older.
 - (2) The relationship between systolic and diastolic blood pressures and cardiovascular events is more pronounced among persons aged 65 years and older. The association is stronger and more consistent for systolic blood pressure than for diastolic blood pressure and is evident at levels considerably < 140 mm Hg.
2. **Rate of cardiovascular events.** Elevations in diastolic or systolic blood pressure values translate into significant increases in cardiovascular events. Generally, the yearly percent risk of cardiovascular events (i.e., risk of event by end of study, divided by duration of study) is between 0.5% and 2.5% for hypertensive subjects aged 40 years or older. Beginning at 115/75 mm Hg, each increase in blood pressure of 20/10 mm Hg doubles the risk of cardiovascular disease.
3. **Systolic blood pressure is a greater predictor of risk.** Over the last few years, **greater emphasis has been placed on systolic blood pressure in characterizing cardiovascular risk.** Age-adjusted 10-year mortality in the MRFIT revealed systolic blood pressure to be a stronger predictor of events from CAD than diastolic blood pressure. High systolic blood pressure conferred a CAD risk regardless of diastolic blood pressure. A systolic blood pressure of 140 to 149 mm Hg confers greater CAD mortality risk than a diastolic blood pressure of 90 to 94 mm Hg. A systolic blood pressure of 150 to 159 mm Hg carries greater risk than a diastolic blood pressure of 95 to 100 mm Hg. According to the SHEP study, isolated systolic HTN, which accounts for 60% of cases of HTN among the elderly, is highly correlated with cardiovascular disease and it is important that it is controlled.
- C. **Clinical presentation.** Detection of HTN begins with proper **blood pressure measurements**, which should be obtained at each health-care encounter.

1. Data for evaluation are acquired through the medical history, physical examination, laboratory tests, and other diagnostic procedures. Evaluation of patients with documented HTN has the following three objectives:
 - a. To identify known causes of high blood pressure
 - b. To assess the presence or absence of end-organ damage and cardiovascular disease, the extent of the disease, and response to therapy
 - c. To identify other cardiovascular risk factors or concomitant disorders that may define prognosis and guide treatment
2. A **medical history** should focus on identifying important risk factors or symptoms of HTN.
3. Repeated **blood pressure measurements** determine whether initial elevations persist and necessitate prompt attention, or the blood pressure has returned to normal and the patient needs only periodic surveillance. Ambulatory blood pressure monitoring is clinically helpful and is most commonly used to evaluate patients with suspected “office” or “white-coat HTN.” It is also helpful in the care of patients with apparent drug resistance, hypotensive symptoms with anti-hypertensive medications, episodic HTN, and autonomic dysfunction.
 - a. **Office visits.** Clinicians should explain to patients the meaning of their blood pressure readings and advise them of the **need for periodic remeasurement**. Blood pressure is measured in a standardized manner with equipment that meets certification criteria.
 - (1) The patient sits in a chair with her or his back supported and the arms bared and supported at heart level.
 - (2) Patients should refrain from smoking or ingesting caffeine during the 30 minutes preceding the measurement.
 - (3) Measurement should begin after at least 5 minutes of rest.
 - (4) The appropriate cuff size must be used to ensure accurate measurement. The bladder within the cuff should encircle at least 80% of the arm. Many adults need a large adult cuff.
 - (5) Measurements are taken preferably with a mercury sphygmomanometer. Otherwise, a recently calibrated aneroid manometer or a validated electronic device can be used.
 - (6) The systolic blood pressure and diastolic blood pressure are recorded. The first appearance of sound is used to define systolic blood pressure. The disappearance of sound is used to define diastolic blood pressure.
 - (7) Two or more readings separated by 2 minutes should be averaged. If the first two readings differ by > 5 mm Hg, additional readings should be obtained and averaged.
 - b. **Ambulatory blood pressure monitoring.** A variety of commercially available monitors that are reliable, convenient, easy to use, and accurate are available. These monitors are typically programmed to take readings every 15 to 30 minutes throughout the day and night while patients go about their normal daily activities. The readings can be downloaded for computer analysis.
 - (1) **Normal** ambulatory blood pressure values are **lower than clinical readings while patients are awake** ($< 135 / < 85$ mm Hg) and are **even lower while patients are asleep** ($< 120 / < 75$ mm Hg). The blood pressure often falls by 10% to 20% during the night. This change is more closely related to patterns of sleep and wakefulness than to the time of day.
 - (2) **Patients with HTN.** Ambulatory blood pressure correlates more closely than clinical blood pressure with a variety of measures of end-organ damage or left ventricular hypertrophy (LVH). Prospective evidence suggests that among patients for whom an elevated clinic pressure is the only abnormality, ambulatory monitoring may help identify a group at relatively low risk for morbidity.

4. **Physical examination** should include the following components:
 - a. **Funduscopic examination** for hypertensive retinopathy (e.g., arteriolar narrowing, focal arteriolar constrictions, arteriovenous crossing changes, hemorrhages and exudates, and disk edema).
 - b. Examination of the **neck** for carotid bruits, distended veins, or an enlarged thyroid gland.
 - c. Examination of the **heart** for abnormalities in rate and rhythm, increased size, precordial heave, clicks, murmurs, and S_3 and S_4 .
 - d. Examination of the **lungs** for rales and bronchospasm.
 - e. Examination of the **abdomen** for bruits, enlarged kidneys, masses, and abnormal aortic pulsation. Abdominal bruits, particularly those that lateralize to the renal area and/or have a diastolic component, suggest renovascular disease. Abdominal or flank masses may indicate polycystic kidneys.
 - f. Examination of the **extremities** for diminished or absent peripheral arterial pulsations, bruits, hair loss, and edema. Delayed or absent femoral arterial pulses and decreased blood pressure in the lower extremities may indicate aortic coarctation.
 - g. **Neurologic assessment.**
 - h. **Other assessments.** Labile HTN or paroxysms of HTN accompanied by any or all of the following symptoms and signs—chest discomfort (“pressure”), headache (“pain”), palpitations, pallor, and diaphoresis (“perspiration”)—may indicate the presence of a pheochromocytoma. Truncal obesity with purple striae suggests Cushing’s syndrome.

D. Laboratory evaluation

1. It is recommended that the clinician request routine laboratory tests before initiating therapy to determine the presence of end-organ damage and other risk factors. These include **urinalysis, complete blood cell count, blood chemistry, and 12-lead electrocardiogram (ECG)**.
2. Additional diagnostic procedures may be indicated to seek causes of HTN: poor response to drug therapy, well-controlled patients whose blood pressures begin to increase, and those with sudden onset of HTN. **Optional tests** include creatinine clearance; microalbuminuria, 24-hour urinary protein, blood calcium, uric acid, fasting triglyceride, low-density-lipoprotein cholesterol (LDL-C), glycosylated hemoglobin, and thyroid-stimulating hormone levels; and limited echocardiography to determine the presence of LVH.
 - a. **Clues from laboratory tests** include unprovoked hypokalemia (i.e., primary aldosteronism), hypercalcemia (i.e., hyperparathyroidism), and elevated creatinine or abnormal urinalysis (i.e., renal parenchymal disease).
 - b. The **presence of LVH** as determined by ECG or echocardiography is an important risk factor for adverse cardiovascular events and an independent predictor of high risk for CAD, cardiovascular disease, and all-cause mortality. LVH, the consequence of chronic pressure or volume overload and obesity, seems to be a stronger predictor of MI and CAD death than the degree of HTN. LV mass, as assessed with echocardiography, is a powerful predictor of cardiovascular events, cardiovascular mortality, and all-cause mortality.
3. **More complete assessment** of cardiac anatomy and function by means of conventional echocardiography, examination of structural alterations in arteries by means of ultrasonography, measurement of ankle–arm index, and plasma renin activity and urinary sodium determinations may be useful in assessing **cardiovascular status** in select patients.

E. Risk stratification

1. **Classification of blood pressure** is given in Table 44.1. The criteria are limited to patients not taking antihypertensive medication and without acute illness. Classification is based on the average of two or more blood pressure readings. When systolic blood pressure and diastolic blood pressure fall into different categories, **the higher pressure should be selected** to classify the patient’s blood pressure.

TABLE 44.1. Classification of Blood Pressure for Adults Aged 18 Years and Older

Category	Systolic blood pressure (mm Hg)		Diastolic blood pressure (mm Hg)
Normal	< 120	and	< 80
Prehypertension	120–139	or	80–89
Stage 1 hypertension	140–159	or	90–99
Stage 2 hypertension	≥ 160	or	≥ 100

2. Risk for cardiovascular disease among patients with HTN is determined by the **blood pressure level** and by the **presence or absence of end-organ damage or other disease-modifying risk factors** (smoking, dyslipidemia, and diabetes). The presence or absence of these factors is determined during the routine evaluation of patients with HTN (e.g., history, physical examination, and laboratory tests). This classification stratifies patients with HTN into risk groups for therapeutic decisions. The World Health Organization Expert Committee on Hypertension Control recommends a similar approach. Obesity and physical inactivity are also predictors of cardiovascular risk and interact with other risk factors, but they are of less importance in the selection of antihypertensive drugs.
 - a. **Risk group A** includes patients with prehypertension or HTN at stage 1 or 2 who do not have clinical cardiovascular disease, end-organ damage, or other risk factors. Persons with stage 1 HTN in risk group A are candidates for a longer trial (up to 1 year) of vigorous lifestyle modification with vigilant blood pressure monitoring. If the desired blood pressure is not achieved, pharmacologic therapy is added. For those with stage 2 HTN, drug therapy is warranted.
 - b. **Risk group B** includes patients with HTN who do not have clinical cardiovascular disease or end-organ damage but have one or more of the risk factors except for diabetes mellitus. This group includes most patients with high blood pressure. If multiple risk factors are present, clinicians consider antihypertensive drugs as initial therapy. Lifestyle modification and management of reversible risk factors are strongly recommended.
 - c. **Risk group C** includes patients with HTN and clinically manifested cardiovascular disease or end-organ damage. According to Joint National Committee 7 (JNC 7) criteria, some patients who fall into the prehypertensive category and have renal insufficiency or diabetes mellitus should be considered for prompt pharmacologic therapy. Appropriate lifestyle modifications are always recommended as adjunct treatment.
 - d. **Therapy.** Antihypertensive treatment has proved **beneficial in the prevention and reduction of the progression of HTN, CVAs, congestive heart failure (CHF), renal insufficiency, and renal failure**. Among patients with mild to moderate HTN, antihypertensive therapy has not favorably influenced angina, MI, and other atherosclerotic diseases (e.g., PVD and aortic atherosclerosis). The lower-than-expected reduction in CAD risk in most trials of antihypertensive agents has been attributed to the choice of agents, such as thiazide diuretics and β -blockers, that might negatively influence risk for CAD and to the short duration of the trials. Overall, antihypertensive treatment markedly reduces the prevalence of CAD events: CAD mortality (by 16%), the rate of fatal stroke (by 40%), and the incidence of heart failure (by 50%), with similar numbers of deaths prevented.

1. Nonpharmacologic therapy

- a. **Weight reduction** reduces systolic and diastolic blood pressures. Most clinical trials have demonstrated that weight reduction is directly related to blood pressure reduction. A weight loss of approximately 10 lb (4.5 kg) may reduce both systolic and diastolic blood pressures by 2 to 3 mm Hg. Among patients with high-normal blood pressure, the need for medical therapy may be averted for one-half through weight reduction by means of physical activity and calorie restriction.
- b. **Exercise** reduces blood pressure by means of decreasing resting heart rate and peripheral vascular resistance and by modifying serum norepinephrine and insulin levels. After an increase in physical activity, both systolic and diastolic blood pressures have been demonstrated to fall by 7 mm Hg with or without weight reduction. Moderate-intensity exercise is as effective as high-intensity exercise for reducing blood pressure.
- c. **Diet.** A modest, independent benefit of **salt reduction** has been demonstrated. HTN is less common in societies that consume low-salt, high-potassium diets. Although the theory that excessive salt intake produces HTN has been difficult to prove in large clinical trials, most data support the role of dietary salt excess for some persons. In general, low-salt diets, such as the Dietary Approaches to Stop Hypertension (DASH; 2,300- and 1,500-mg sodium diets), are recommended to most patients with HTN. Pooled estimates have suggested that **salt restriction is most important for older persons, those with higher baseline levels of blood pressure, and particularly those who are salt sensitive**. Salt restriction reduces the need for combination antihypertensive medications.
- d. Tobacco and immoderate alcohol use (more than two daily drinks for men and more than one daily drink for women) increase blood pressure. **Cessation of smoking and excessive alcohol use** markedly reduces blood pressure and further reduces cardiovascular risk.

2. Medical therapy

a. Priority of therapy

- (1) Therapy for most patients with **uncomplicated HTN** at stage 1 should **begin with the lowest dose** to prevent adverse effects. If blood pressure remains uncontrolled after 1 to 2 months, the next dose level may be prescribed. It may take months to adequately control HTN. Most antihypertensive agents may be taken once each day. To improve patient compliance, this regimen is used whenever possible.
- (2) For patients at **higher risk**, those in risk group 2, or those at particularly high risk for CAD or CVA event, drug therapy to **achieve maximum beneficial reductions** in blood pressure should **proceed without delay**. If blood pressure is elevated by 20/10 mm Hg above the goal, guidelines recommend starting two agents simultaneously.
- (3) There is **no debate regarding the need for aggressive blood pressure reduction** in patients with **diastolic blood pressures > 115 mm Hg and systolic blood pressures > 160 mm Hg**. JNC 7 aggressively targets the 140/90 mm Hg cut-point and incorporates hypertensive therapy into an algorithm of overall risk.
- (4) In the setting of hypertensive emergency (**HTN with end-organ damage, often with neurologic symptoms**), patients with a systolic blood pressure > 200 mm Hg or a diastolic blood pressure > 120 mm Hg may need **hospitalization** for therapy.
- (5) Although some patients may respond to single therapy, **two or more drugs are often required**. The intervals between changes in regimen should not be prolonged, and the maximum dose of some drugs may be increased.

- b. Medication selection.** Special considerations include concomitant disease, demographic characteristics, quality of life, cost, and use of other drugs that may cause drug interactions.

(1) Concomitant diseases (see Table 44.2). Antihypertensive medications may worsen some diseases and improve others. Agent selection involves consideration of coexisting disease, simplification of regimens, and reduction of cost. Special emphasis should be given to diabetes and chronic renal disease. Such patients should be aggressively treated to maintain a goal blood pressure of $< 130/80$ mm Hg.

(a) Reduction of long-term cardiovascular morbidity and mortality.

Diuretics and β -blockers were drug classes originally shown in randomized trials to reduce morbidity and mortality. The Heart Outcomes Prevention Evaluation (HOPE) trial demonstrated that angiotensin-converting

TABLE 44.2. Management of Hypertension in Specific Clinical Syndromes

Condition	Treatment
Acute coronary syndrome	β -Blockers or nitrates; CCB
Hypertension among African Americans	Diuretic or CCB
Arrhythmia	
Sinus bradycardia, SSS, or AV block	Diuretic, ACE inhibitor, or α -blocker
Atrial fibrillation or flutter and SVT	β -Blocker, diltiazem, verapamil, or clonidine
Benign prostatic hypertrophy	α -Blocker
COPD with bronchospasm or asthma	CCB or ACE inhibitor
Diabetes	ACE inhibitor
Advanced age (> 65 y)	Diuretic, CCB, or ACE inhibitor at lower doses to avoid postural hypotension
Gout	Any <i>except</i> diuretics
Congestive heart failure	
Systolic	ACE inhibitor, diuretic, β -blockers
Diastolic	CCB or β -blockers
HOCM	β -Blockers or verapamil
Liver dysfunction	Any <i>except</i> methyldopa and labetalol
Post–myocardial infarction	ACE inhibitor, β -blocker, or both
Osteoporosis	Thiazide diuretics
PVD	Vasodilator, ACE inhibitor, CCB, or α -blocker
Renal insufficiency (creatinine > 2 mg/dL)	Loop diuretics, ACE inhibitor, CCB, α -blocker, labetalol, or a combination of these
Diabetic nephropathy	ACE inhibitor
Smokers	α -Blockers, ACE inhibitors, or CCB
Isolated systolic hypertension	Diuretics, CCB, and ACE inhibitors

ACE, angiotensin-converting enzyme; AV, atrioventricular; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; HOCM, hypertrophic obstructive cardiomyopathy; PVD, peripheral vascular disease; SSS, sick sinus syndrome; SVT, supraventricular tachycardia.

enzyme (ACE) inhibitors reduced the risk of cardiovascular events in patients with vascular disease or diabetes plus one other cardiovascular risk factor. However, the fact that HOPE was a trial with placebo control rather than active control suggests that blood pressure lowering, and not drug class effect, may have been responsible for the improved outcomes. The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) study showed a preferential reduction in cardiovascular events with the angiotensin receptor blocker losartan compared with atenolol in hypertensive patients. This improvement was primarily driven by a reduction in the number of strokes in the losartan group.

- (b) **Regression of LVH** has been associated with a reduction in risk for cardiovascular events. All commonly used antihypertensive strategies, with the exceptions of direct vasodilators and weight loss, induce regression of LVH. Specifically, the ACE inhibitor ramipril has been shown to cause regression of electrocardiographic markers of LVH, with an associated reduction in death, MI, stroke, and CHF. The LIFE trial demonstrated a superiority of the angiotensin II receptor blocker losartan over the β -blocker atenolol in the absence of LVH regression, suggesting that LVH might not be as powerful a surrogate of risk as initially thought. Further study of this issue is needed.
- (2) **Dosage.** For most patients, a **low dose of the initial drug** choice is initiated and then titrated to the desired effect. The optimal formulation provides 24-hour efficacy with a once-daily dose, with at least a 50% of the peak effect remaining at the end of 24 hours. Long-acting formulations increase adherence, reduce cost, provide consistent blood pressure control, and protect against early-morning sudden death. Diurnal blood pressure control is reported to improve when long-acting medication is taken at night rather than in the morning.
- (3) **Special populations.** Neither sex nor age usually affects responsiveness to various agents. In general, HTN among **African Americans** is more responsive to monotherapy with diuretics and calcium channel blockers than with β -blockers or ACE inhibitors. However, if a β -blocker is needed for other therapeutic benefits, then differences in efficacy can usually be overcome with reduction of salt intake, higher doses of the drug, or addition of a diuretic.
- (4) **Drug interactions.** Some drug interactions may be beneficial. For example, diuretics acting on different sites in the nephron may increase natriuresis and diuresis. Diltiazem may reduce the amount of cyclosporine needed in transplant recipients. Other interactions may be harmful. Nonsteroidal anti-inflammatory drugs may blunt the action of diuretics, β -blockers, and ACE inhibitors.
- c. **Treatment of the elderly.** The benefit of blood pressure lowering is evident in the elderly, with a marked **reduction in all-cause mortality and CAD mortality**, as shown in multiple trials and studies. SHEP was the first study to show that antihypertensive treatment of the elderly can reduce these events. It is not clear, however, that all agents are equally effective in reducing the rate of cardiovascular events in the elderly.
- d. **Emerging evidence.** The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the incidence of cardiovascular events in hypertensive patients treated with a thiazide-type diuretic (chlorthalidone), calcium channel blocker (amlodipine), or ACE inhibitor (lisinopril) who were followed over 5 years. A fourth arm of the trial consisting of treatment with the α -blocker doxazosin had been stopped prematurely because of increased cardiovascular events, specifically a doubling in the risk

of CHF in the doxazosin arm compared with the chlorthalidone arm. The results indicated no difference in the three remaining groups regarding the primary outcome of combined fatal coronary heart disease or nonfatal MI. Chlorthalidone was superior to amlodipine in preventing heart failure and superior to lisinopril in preventing stroke and combined cardiovascular disease. Given their clear efficacy, relatively low cost, and high tolerability, thiazide diuretics are therefore considered initial agents of choice for most patients with HTN and core components of multidrug regimens.

III. OBESITY. Rates of obesity are rising at an alarming rate both in the severe obesity cases (body mass index [BMI] $> 40 \text{ kg/m}^2$) and in adolescents. Currently, 66% of US adults are overweight, defined as having a BMI of $> 25 \text{ kg/m}^2$. Moreover, 32% of Americans are classified as obese, with a BMI of 30 kg/m^2 or more. This has come to be a critical problem for African American women, among whom the prevalence of obesity is $> 50\%$. The percentage of children and adolescents with obesity has doubled over the last 20 years. There are clear links between obesity and the development of cardiac risk factors: HTN, hyperlipidemia, and diabetes.

A. Link between obesity and cardiovascular disease

1. A positive association among BMI, increased total cholesterol and triglyceride levels, and a decreased high-density-lipoprotein cholesterol (HDL-C) levels has been documented in various age groups.
2. Distribution of fat appears to be a more important predictor of CAD than the total amount of fat because android fat patterns are more metabolically active and highly associated with dyslipidemia. Although BMI and waist-to-hip ratios have indicated a linear association between obesity and CAD, the **waist-to-hip ratio**, which accounts for abdominal adiposity, is viewed as a more **accurate predictor of CAD**. Among obese persons, those with central adiposity are at particularly high risk. In a cohort of 1,500 women observed for 20 years, the waist-to-hip ratio, but not BMI, was highly predictive of the occurrence of fatal MI.
3. The **National Center for Health Statistics still uses BMI**, defined as **weight (kg)/height (m^2), as the recognized measurement of obesity**. Their guidelines define obesity as a BMI of 27.8 kg/m^2 or more for men and 27.3 kg/m^2 or more for women. Morbid obesity has been defined as a BMI of 31.1 kg/m^2 for men and 32.3 kg/m^2 for women. The Nurses' Health Study showed that women with a BMI of 25 to 29 kg/m^2 had an age-adjusted relative risk for CAD of 1.8 compared with the leanest women. Women with a BMI $> 29 \text{ kg/m}^2$ had a relative risk for CAD of 3.3.
4. Obesity among adults is associated with **increased LV mass**, a powerful independent predictor of mortality and morbidity from cardiovascular disease. LV mass in persons with obesity but without diabetes probably depends, at least in part, on the degree of insulin resistance and hyperinsulinemia and not on BMI and blood pressure.
5. Central obesity is part of the **metabolic syndrome**, which appears to be associated with increased risk for CAD in both sexes. This condition is characterized by elevated plasma triglyceride and low plasma HDL-C levels.
 - a. An essential feature is the presence of **dense, atherogenic LDL**.
 - b. Other features are HTN, impaired glucose intolerance with hyperinsulinemia, and decreased sensitivity to the action of insulin on peripheral tissues.
 - c. Hyperinsulinemia is associated with **lipid derangements, increased production of plasminogen activator inhibitor, and enhanced proliferation of cells in atherosclerotic plaque**. Among patients with hyperinsulinemia, an increased prevalence of CAD and a relationship among abnormal insulin levels, glucose metabolism, and severity of CAD have been reported. The physiologic response to insulin resistance is increased secretion of insulin, which may lead to glucose intolerance or frank diabetes mellitus.

B. Therapy

1. **Calorie restriction, behavior modification, and exercise** are the main treatment modalities for weight loss. The greatest weight losses have occurred with a combined regimen of diet and exercise rather than diet or exercise alone.
2. Several **medications** can be used for the temporary management of obesity. Although pharmacologic agents temporarily aid in the struggle against obesity, the National Task Force on Obesity **cautions against the use of these agents for long-term maintenance because of the potential for unknown side effects.**
 - a. **Noradrenergic drugs** influence weight loss through stimulation of the hypothalamus.
 - b. **Orlistat**, a pancreatic lipase inhibitor, reduces weight through inhibition of fat absorption.
 - c. **Serotonin reuptake inhibitors**, including sibutramine, fluoxetine, and sertraline, promote weight loss with various degrees of side effects.
 - d. Use of dexfenfluramine and fenfluramine, already of concern because of rare instances of pulmonary HTN, has been discontinued because of associated acquired valvular heart disease.
3. In the most extreme cases, **surgical therapy** can be provided. Among morbidly obese patients (BMI > 40 kg/m²) and obese patients (BMI between 35 and 40 kg/m²) with coexisting conditions, jejunoileal shunts and gastropasty often aid in the maintenance of weight loss. About 10 years after surgical intervention, 80% of patients maintain a weight 10% less than preoperative weight.
4. **Risk of weight loss.** Even if weight is lost, weight loss maintenance fails in most instances. Health risks that accompany weight cycling are increases in cardiovascular morbidity and mortality, abdominal fat, blood pressure, and insulin resistance.

IV. TOBACCO. Smoking, the single most preventable cause of death in the United States, is a leading risk factor for CAD, CVA, and PVD. Second-hand smoke has been shown to increase the risk for CAD. The causal role of smoking in cardiovascular disease has been derived from > 20 million person-years of follow-up study (NHLBI, 1996). Twenty-eight percent of white men and 25% of white women smoke, as do 34% of African American men, 22% of African American women, 24% of Hispanic men, and 15% of Hispanic women. It is estimated that 37% of the population is exposed to second-hand smoke. Exposure to second-hand smoke increases the risk of death from CAD by 30%. More than 90% of current smokers began their habit before they were 21 years of age.

- A. **Pathophysiology.** Cigarette use activates platelets, increases circulating fibrinogen, increases heart rate, and elevates blood pressure. It appears to promote plaque disruption. A strong dose–response relationship exists between smoking and CAD. Duration of smoking and the daily amount markedly influence the risk of CAD. The number of cigarettes smoked per day is directly proportional to the risk of MI. The adverse effect of smoking is present among men and women (but may be stronger among women) of all ages and ethnic groups with or without prior CAD. Data suggest that risk for cardiac death is two to four times greater among current smokers than nonsmokers.
- B. **Risk reduction and therapy.** **Risk for cardiovascular disease begins to decline soon after smoking cessation**, irrespective of age and sex. There is a 50% reduction in cardiovascular events within the first 2 to 4 years of cigarette cessation; however, increased cardiovascular risk still exists 10 years after cessation. It is thought to take as long as 20 years to regain baseline risk.
 1. **Behavioral and psychosocial treatment.** Several techniques have been developed to help patients stop smoking and maintain cessation. These have variable effect.
 2. **Pharmacotherapy**
 - a. **Nicotine replacement therapy (NRT).** Approximately 50% to 70% of patients discontinue cigarette use after a major cardiac event, such as MI or coronary artery bypass grafting. Cessation for another 10% to 20% can be accomplished with cigarette cessation programs, which often incorporate

nicotine patches or the somewhat less efficacious nicotine gum. Programs that incorporate a nurse clinician increase cessation rate beyond 30%. An 8-week treatment appears to be as effective as longer periods of use.

- (1) **The patch.** Clinical practice guidelines support the use of transdermal nicotine patch as the **primary pharmacologic agent for all patients who smoke**. The risk of use of the patch among patients with CAD is now considered to have been overstated. Use of the patch is contraindicated in persons who continue to smoke because it leads to nausea. **Side effects** of NRT include itching and skin rash among as many as 50% of patients. NRT approximately doubles cessation rate. One-year follow-up evaluations of patch-cessation therapy indicated cessation rates of 20% to 25% compared with 5% to 10% for a placebo.
 - (a) Standard dosages (Nicoderm, Prostep, and Nicotrol) include the maximum doses for 4 weeks and lesser doses for another 4 weeks.
 - (b) Because baseline nicotine levels (i.e., the number of cigarettes smoked per day) are inversely associated with cessation rates, **patients who smoke < 1 pack per day** may be adequately treated with **submaximal nicotine doses**.
- (2) **Nicotine gum.** Use of gum for NRT appears to delay post-cessation weight gain, a typical deterrent to cigarette cessation. Multipack users should use 4 mg gum, whereas patients who smoke < 1 pack per day may need only 2 mg.
- (3) **Nicotine nasal spray** has been approved as a smoking cessation treatment. Nasal spray provides a more rapid rise in nicotine level than that with gum or patch, with peak levels occurring in < 10 minutes. Nicotine nasal spray has markedly more severe **side effects** and appears to be best suited for patients who have not had success with other forms of NRT.
- b. **Other pharmacologic agents.** For select patients, supplementation with agents other than NRT may be useful, even though NRT is the only strategy recommended in standard smoking cessation guidelines.
 - (1) **Bupropion**, which is approved for smoking cessation, has dopaminergic and noradrenergic properties. Clinical trials have demonstrated the efficacy of bupropion sustained release (SR) with or without transdermal nicotine for smoking cessation. The recommended dosage of bupropion is 150 mg two times per day. In clinical trials, the medication was typically started 1 to 2 weeks before cessation and was continued for 7 to 12 weeks after cessation. Abstinence rates at 12 months were 30% for patients treated with bupropion for 9 weeks in one study, and combination therapy with bupropion and a nicotine patch resulted in a 35.5% abstinence rate.
 - (2) Bupropion must be **avoided by patients with a seizure disorder or who are at risk for seizures** (i.e., patients with head injury, those who abuse alcohol, or those who have alcohol dependence) because the medication lowers seizure threshold. Common **side effects** of bupropion include headache, nausea, and restlessness. Bupropion has no serious adverse effects on the cardiovascular system.
 - (3) **Clonidine**, an α_2 -agonist, **dampens the sympathetic activity associated with withdrawal**. Dosages used for smoking cessation typically range from 0.1 to 0.4 mg/d for 2 to 6 weeks in the oral or the transdermal preparation. The most common **side effects** are dry mouth, constipation, postural hypotension, and sedation. Clonidine is **recommended for patients who prefer not to take or who have not had success with NRT**. Nasal spray clonidine has been effective among nicotine-dependent women who are intolerant of the patch.
 - (4) **Varenicline** is a partial agonist of the nicotinic acetylcholine receptor, in particular, the $\alpha_{4\beta 2}$ subtype. Several trials have demonstrated improved

efficacy in achieving smoking cessation when compared with NRT and bupropion SR. However, because of case reports of adverse psychiatric behavior occurring during varenicline administration, including suicidal ideation, suicidal behavior, and erratic behavior, practitioners are encouraged to monitor their patients closely for signs of psychiatric changes.

V. SEDENTARY LIFESTYLE

A. Pathophysiology. A sedentary lifestyle is associated with increased risk for CAD. Sedentary persons have almost double the risk for CAD death as that of active persons. In five prospective exercise studies, persons at the lowest levels of exercise conditioning had an age-adjusted CAD mortality risk 2 to 10 times that of the best-conditioned participants. Meta-analyses of epidemiologic studies suggest a nearly twofold increase in risk among sedentary persons for development of CAD and for CAD death. A sedentary lifestyle is also associated with obesity, HTN, diabetes mellitus type 2, and hypercholesterolemia, which point to the need for changes in exercise patterns. More than 50% of the US population do not exercise at least 20 minutes three times a week and 40% of adults are classified as sedentary. Only 22% of US adults partake in 30 or more minutes of exercise five times a week and 25% report no leisure-time physical activity.

B. Risk reduction. Even moderate physical activity provides a reduction in risk. Regular physical activity prevents obesity, may reduce weight, and promotes positive effects on blood pressure, LDL-C, HDL-C, and triglyceride levels. Independent of other risk factors, physical fitness has a direct protective effect against CAD events. Among patients who have had MI, controlled cardiac rehabilitation programs significantly reduce cardiovascular mortality by 20% to 25%. The American Heart Association (AHA) currently recommends that adults accumulate 30 minutes or more of moderate-intensity physical activity on most (preferably all) days of the week.

1. Mechanism

a. Exercise **improves glucose tolerance and insulin sensitivity, increases fibrinolysis, increases HDL-C levels, improves oxygen uptake** in the heart, and **increases coronary artery diameter**. Exercise reduces the sensitivity of the myocardium to catecholamines and the risk of ventricular arrhythmias. Exercise increases HDL-C and lowers LDL-C levels and, as such, reduces cardiac events. Exercise can alter the progression of coronary atherosclerosis. Among patients with angiographically documented CAD, exercise training may increase regression and reduce the progression of coronary lesions.

b. Studies on the effect of exercise have been difficult to conduct and are known to have difficulties in quantification of exercise. Reviews on the effects of cardiac rehabilitation on morbidity and mortality demonstrated reductions in all-cause mortality of 20% to 24% and in CAD mortality of 23% to 25%. The data support a reduction in anginal episodes and mortality, although the reduction in mortality is no better than 15%. A direct relationship has been shown between exercise intensity and angiographic modifications: 1,533 kcal/wk is necessary to stabilize coronary lesions and 2,200 kcal/wk is needed to induce coronary regression.

2. Fitness (measured in metabolic equivalents or METs achieved) and **physical activity** (measured in caloric expenditure per time period) appear to be closely linked, although it remains unclear which of the two is the better predictor of cardiovascular morbidity and mortality.

a. Several studies have shown that **higher degrees of physical activity** are associated with decreased risk for death from CAD. There is an inverse association between the increasing physical activity (measured in MET-hours/week) and the risk of cardiovascular events. These studies suggest that **changes in fitness from low to high levels and level of current activity are the best predictors of reduction in risk for CAD**.

- b. **The death rate decreased by 50% among men** 60 years or older who changed from unfit to fit status over an 18-year follow-up period. The age-adjusted cardiovascular disease mortality rate decreased by 52%.
 - c. An important measurement of fitness among **older postmenopausal women** is leisure-time physical activity; it can substantially reduce the risk of MI. Even moderate-intensity exercise has been shown to confer substantial benefits for postmenopausal women. Such women who walk or exercise vigorously at least 2.5 hours each week have been shown to have a cardiovascular risk reduction of approximately 30%.
3. **Problems with compliance.** Only 50% of persons who begin an exercise program adhere to it for more than 6 months.
- a. Physicians may need to help **tailor exercise programs for individual patients** to participate in activity that is sustained in the long-term.
 - b. As for healthy persons, **precautions** must be taken to **prevent injury**. The current guidelines may be **slightly modified for elderly exercisers** to emphasize a longer warm-up period to enable musculoskeletal and cardiorespiratory readiness for exercise and an adequate cool-down period to help dissipate heat.

VI. NOVEL RISK FACTORS. Screening studies have shown that HTN, hyperlipidemia, tobacco use, family history, and diabetes are predictive of less than half of all future cardiovascular events. Among patients with premature atherosclerosis, the predictive value of these traditional cardiovascular risk factors is limited. Many patients with few traditional risk factors experience life-threatening acute coronary syndromes without prior symptoms of disease. Several potential risk factors have been identified that may enhance risk for CAD. These are levels of C-reactive protein (CRP), lipoprotein(a) or Lp(a), homocysteine, fibrinogen, and myeloperoxidase (MPO), as well as genetic mutations and single-nucleotide polymorphisms (SNPs) in a number of candidate genes.

A. CRP is a marker of systemic inflammation. As the role of **inflammation** in the initiation and progression of atherosclerosis becomes better understood, CRP is gaining prominence as an important player in the assessment of cardiovascular risk.

1. Pathophysiology

- a. CRP has been shown to be an independent risk factor for the development of cardiovascular events in both apparently healthy individuals and in patients with established coronary heart disease. The exact role that CRP plays in this association has not yet been well characterized. Initially, it was believed that CRP provided an indirect measurement of the inflammatory milieu in at-risk individuals. Emerging evidence, however, indicates that CRP itself may have a direct causal influence on the development of atherosclerosis. CRP binds to oxidized LDL, promoting the uptake of LDL by macrophage scavenger cells in the arterial wall and possibly enhancing the atherosclerotic process.
- b. The degree of associated risk throughout various levels of CRP, often measured as high-sensitivity C-reactive protein (hsCRP), has been evaluated in several studies.
 - (1) Men in the Physicians' Health Study with the highest quartile CRP had **three times the risk of MI** and **twice the risk of ischemic stroke** compared with men in the lowest quartile.
 - (2) In women, the difference is even more pronounced. The relative risk of cardiovascular events in the highest quartile of CRP compared with the lowest quartile of CRP in women is **4.4**.
 - (3) An increased risk of sudden cardiac death has also been seen in patients with elevated CRP levels.

2. Clinical use

- a. Standard CRP assays are not sufficiently sensitive to discriminate within the narrow range of CRP values associated with an increase in cardiovascular events. The development of hsCRP assays, however, has made this possible.

AHA/Centers for Disease Control and Prevention (CDC) guidelines have established cut-points of risk for hsCRP: a level of < 1 mg/L is considered low, 1.0 to 3.0 mg/L is average, and > 3.0 mg/L is high and is associated with increased cardiovascular risk. Higher levels (> 10 mg/L) suggest an alternative cause for inflammation, such as infection or underlying rheumatologic illness.

- b. When deciding on whether to initiate statin therapy for the primary prevention of coronary events, hsCRP measurement may prove helpful in patients with a moderate level of cardiovascular risk (calculated 10-year major cardiac event risk of 10% to 20%). If found to have an elevated hsCRP level, these patients may benefit from a more intensified therapy, including dietary modifications and, perhaps, statin therapy. In the Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), lovastatin reduced the incidence of cardiovascular events in patients with low lipid levels if CRP levels were elevated. No improvement was seen in the cohort of patients with low lipid levels and normal CRP values. The Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial (JUPITER) study targeted individuals with elevated hsCRP levels without hyperlipidemia and showed that statin therapy substantially lowered cardiovascular events in this population.
 - c. The AHA/CDC panel recommends against widespread screening of the general population. In secondary prevention, hsCRP assessment can be performed, but proven intensified therapy (including statins) should not be withheld based on the level of hsCRP attained. Serial hsCRP measurements should not be used to monitor the effects of lipid treatment.
3. **Risk reduction and therapy.** Weight loss with caloric-restriction diets has been shown to decrease plasma CRP levels. Additional data indicate that women who exercise regularly have lower CRP levels compared with sedentary women. In primary prevention trials, pravastatin has been shown to reduce CRP levels by about 17%, in a manner independent of LDL lowering. Evidence suggests that simvastatin lowers CRP within the first 2 weeks of therapy, before any LDL-lowering effect is seen. What is not known, however, is whether reducing CRP by any such means confers an independent benefit in regard to lowering cardiovascular morbidity and mortality.
- B. **Lipoprotein (a) or Lp(a)** is identical to LDL, except for the addition of apolipoprotein A (apoA), a highly glycosylated protein. Although it is a lipoprotein, Lp(a) is often considered a **marker of thrombosis**.
 1. **Pathophysiology**
 - a. There is a striking amino acid sequence homology between apoA and plasminogen, suggesting that Lp(a) may play an important role in the connection between atherosclerosis and thrombosis. **Lp(a) may be atherogenic**; it accumulates in atherosclerotic lesions, binds to apoB-containing lipoproteins and proteoglycans, and can be taken up by foam cell precursors. It may also promote thrombosis when it binds to fibrin and blocks the fibrinolytic action of plasmin.
 - b. Lp(a) may be more predictive of CAD among younger men, women, and persons with hyperlipidemia.
 - c. **Studies have had mixed results**
 - (1) Cross-sectional and retrospective case-control studies have usually supported the role of Lp(a) in CAD. Lp(a) is a marker among patients at particular risk for poor outcomes, in terms of severity and progression of cardiovascular disease.
 - (2) Several prospective studies have correlated baseline Lp(a) levels with vascular disease in general.
 - (3) Other prospective studies have found little or no association between Lp(a) and CAD risk.
 - d. **Few studies** have been conducted on the role of Lp(a) in **women**. Cardiovascular risk tends to increase with an Lp(a) value > 30 mg/dL.

2. **Therapy.** Niacin is the only agent currently available that reduces Lp(a). However, due to the multiplicity of lipid effects exerted by niacin therapy, it is unknown if reduction in Lp(a) levels is beneficial. In addition, the atherogenicity of Lp(a) may be modified through **substantial reductions in LDL-C levels**.
- C. **Homocysteine** is a product of folate metabolism. It is derived from the sulfur-containing amino acid methionine and is metabolized through pathways associated with folic acid, vitamin B₆, and vitamin B₁₂ as cofactors.
 1. **Etiology and pathophysiology**
 - a. Elevated plasma homocysteine levels ($> 15 \mu\text{M}$) confer an **independent risk for vascular disease**, according to the cross-sectional and prospective case-control studies. The risk was first identified because of increased thromboembolic events, including MI and stroke, in patients with **homocystinuria**, a rare inherited deficiency of cystathionine β -synthase characterized by very high serum homocysteine levels ($> 100 \mu\text{mol/L}$).
 - b. Elevated homocysteine levels are found among $> 20\%$ of patients with atherosclerotic disease, including PVD. In PVD, there may be direct endothelial toxicity, smooth muscle cell proliferation, enhanced LDL oxidation, abnormalities in platelet function, or increased thrombotic risk because of abnormal clotting factors (e.g., factor V and factor VII) or altered secretion of von Willebrand's factor.
 - c. The **relative risk of stroke and MI is approximately 2 for homocysteine levels $> 15 \mu\text{mol/L}$** compared with those $< 10 \mu\text{mol/L}$. The relative risk of PVD is much greater than 3. Risk enhancement is continuous over the spectrum of homocysteine values.
 - d. A meta-analysis of case-control observational studies is less compelling. This study examined patients with a genetic polymorphism of an enzyme involved in folate metabolism; this alteration resulted in elevated homocysteine levels. Individuals with this mutation had only a 16% higher risk of developing CHD compared with normal controls.
 - e. **Secondary causes** of increased homocysteine levels include age, male sex, menopause, renal function, and some medications (e.g., niacin, oral contraceptives with estrogen, phenytoin, methotrexate, and theophylline). Thyroid function is also relevant.
 - f. The mechanism by which homocysteine appears to promote vascular disease is **unclear**. Elevated homocysteine levels seem to play a role in the production of arterial lesions, but deficiencies of other factors, such as vitamin B₁₂ and folic acid, may also be involved, especially in the elderly.
 - g. **Possible mechanisms** of increased risk are that hyperhomocysteinemia may impair release of nitric oxide from endothelial cells, stimulate proliferation of atherogenic smooth muscle cells, and contribute to thrombogenesis through activation of protein C.
 - (1) Deficiencies in the cofactors lead to elevated serum concentrations of homocysteine, although profound deficiencies are rare among persons with high homocysteine CAD.
 - (2) Rare defects in the genes for 5,10-methylene tetrahydrofolate reductase, cystathionine β -synthase (0.5% prevalence), methylene tetrahydrofolate homocysteine methyltransferase (rare), and methionine synthases (rare) can lead to increases in homocysteine.
 2. **Laboratory examination.** For patients with abnormal homocysteine values, further evaluation includes thyroid-stimulating hormone, vitamin B₁₂, vitamin B₆, folate, and creatinine.
 3. **Trials of homocysteine lowering.** The results of three such large, prospective, randomized trials have been reported in recent years. In the Vitamin Intervention for Stroke Prevention (VISP) trial, patients with a history of stroke were treated with two different doses of folic acid, vitamin B₆, and vitamin B₁₂.

Although a dose-dependent reduction in homocysteine levels was observed, no difference in vascular events was observed between the two groups. The Norwegian Vitamin Trial (NORVIT) randomized patients with history of MI to four different treatment groups: folic acid, vitamin B₆, and vitamin B₁₂; folic acid and vitamin B₁₂; vitamin B₆ alone; or placebo. After a mean 40 months of therapy, homocysteine levels were decreased by 27% in the group treated with folic acid and vitamin B₁₂. However, these subjects had no difference in the development of the primary end point (recurrent MI, stroke, or sudden death from CAD) compared with the placebo group. In the group treated with all three supplements, there was not only a marginally significant trend toward fewer strokes but also a near-significant trend toward more MIs. Finally, the Heart Outcomes Prevention Evaluation 2 (HOPE-2) trial was a mixed primary and secondary prevention trial, treating vascular disease or diabetic patients with either a combination of folic acid, vitamin B₆, and vitamin B₁₂ or placebo. Despite a significant decrease in homocysteine levels with active treatment, there was no significant difference in the primary outcome (MI, stroke, or death from cardiovascular causes) when compared with placebo treatment. There was a marginally significant decrease in stroke with vitamin administration. It is unknown whether the negative results of these studies result from incorrectness of the homocysteine atherosclerotic hypothesis or from pathologic effects of vitamin therapy offsetting possible benefit of homocysteine reduction. Regardless, given the lack of benefit (and in some cases, suggestion of harm) provided by folic acid with or without B vitamins, such therapy cannot be recommended for the prevention of cardiovascular disease.

D. Fibrinogen, a large hepatically synthesized glycoprotein, is a clotting factor that activates thrombin, induces platelet aggregation through the glycoprotein IIb/IIIa receptor, and stimulates smooth muscle proliferation.

1. Etiology and pathophysiology. There is increasing evidence that **fibrinogen is important in the development of premature atherosclerosis**. The link is likely and plausible.

- a. Several prospective studies, including the Framingham Heart Study, have shown an **impressive relationship between the plasma fibrinogen level and the occurrence of CAD and stroke**. Plasma fibrinogen levels > 350 mg/dL are powerful independent risk factors for stroke and MI. A high fibrinogen level is an independent risk factor for CAD with a twofold to threefold increase in risk and markedly enhances risk for hypercholesterolemia.
- b. Clinical findings suggest that a **high fibrinogen level may also be a risk factor for the sequelae of CAD**. In the Northwick Park Heart Study, a fibrinogen level in the upper third was associated with a three times higher risk for cardiovascular disease than a plasma level in the lower third. In the Göteborg study, baseline fibrinogen level was significantly related to the incidence of MI and ischemic stroke.

2. Cofactors. Determinants of high fibrinogen levels include age, female sex, menopause, African American race, smoking, obesity, stress, use of oral contraceptives, pregnancy, and a consumption of large amounts of dietary fat.

3. Risk reduction and therapy

- a. Factors associated with a decrease in fibrinogen level include smoking cessation, physical activity, moderate alcohol intake, normalization of body weight, and postmenopausal hormone replacement.
- b. Although no clinical trial has identified a drug that reduces fibrinogen level safely and selectively, the following medications have been shown to decrease fibrinogen level in various clinical settings: fibrates, pentoxifylline, ticlopidine, *n-3* polyunsaturated fatty acids, and anabolic steroids.

- E. Myeloperoxidase.** As discussed previously, inflammation plays a major role in the pathogenesis of CAD and the development of MI. MPO is a protein with enzymatic activity that is released during activation and degranulation of neutrophils and monocytes. For patients in the emergency department with chest pain, serum levels of MPO have been shown to predict risk for MI at 30 days and 6 months, even in the absence of myocardial necrosis. In patients with non-ST-elevation MI, MPO levels have recently been shown to predict 30-day risk of recurrent nonfatal MI or hospitalization for acute coronary syndrome.
- F. Nonlipid genetic factors.** Although a familial predisposition for CAD has been well documented, little is known about the causative factors leading to premature events in such kindreds. In one family, a seven-amino acid deletion in the gene encoding the MEF2A transcription factor was found to confer autosomal dominant susceptibility to CAD and MI. The thrombospondins are a family of glycoproteins that play a pivotal role in cell adhesion, vascular integrity, and thrombosis. SNPs in thrombospondin genes have been linked to premature atherosclerosis and MI, providing another example of how genetic variations may contribute to the development of coronary disease. Recently, the general excitement regarding genetics of CAD has been somewhat tempered by publications of negative findings. Nevertheless, the identification of genetic risk factors for cardiovascular disease and the elucidation of their mechanism of risk elevation are still among the newest and most promising areas of translational cardiology research.

ACKNOWLEDGMENTS: *The authors thank Drs. J. Christopher Merritt and JoAnne Micalé Foody for their contributions to earlier editions of this chapter.*

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CHAPTER

45

Amanda R. Vest
Leslie Cho

Diabetes and the Heart

I. INTRODUCTION. The presence of type 1 diabetes mellitus (T1DM) or type 2 diabetes mellitus (T2DM) confers a marked increase of risk of coronary artery disease (CAD) development. **CAD accounts for as many as 80% of deaths among individuals with diabetes, compared with 30% in those without diabetes.** The prevalence of T2DM, which correlates closely with overweight and obesity, has shown a sharp rise over recent decades. Consequently, the management of diabetes, in parallel with the management of nonglycemic CAD risk factors including hypertension, dyslipidemia, and obesity, has become a prime focus in both the primary and secondary prevention of cardiovascular events. Significant uncertainty remains regarding the impact of tight glucose control on future cardiovascular events and the optimal glucose-lowering drug regimen. The revascularization strategies best suited to individuals with diabetes are also an area of ongoing research.

II. EPIDEMIOLOGY

A. Epidemiology of diabetes

1. Diabetes has been described as a worldwide epidemic and is now one of the most common chronic diseases in both developed and developing nations. This rise in prevalence is driven partly by rising levels of obesity, physical inactivity, and

TABLE 45.1 List of Countries with the Highest Numbers of Estimated Cases of Diabetes for 2000 and 2030

2000		2030	
Country	People with diabetes (millions)	Country	People with diabetes (millions)
1 India	31.7	India	79.4
2 China	20.8	China	42.3
3 United States	17.7	United States	30.3
4 Indonesia	8.4	Indonesia	21.3
5 Japan	6.8	Pakistan	13.9

From Wild S, Roglic G, Green A, et al. Global prevalence of diabetes. *Diabetes Care*. 2004;27(5):1047–1053.

urbanization, coupled with the aging population and greater longevity for patients with diabetes due to advances in diabetes management. The International Diabetes Federation reported that there were 30 million individuals with diabetes worldwide in 1985. The most recent analysis of data suggests this had grown to 171 million adults over 20 years in 2000 (1). If the age-specific prevalence remains constant, there will be a projected doubling in global diabetes cases between 2000 and 2030, bringing the expected total to a staggering 366 million.

- The greatest burden of diabetes lies in developing countries, as illustrated in Table 45.1. India and China are notable for the exceptionally high prevalence in 2000 (31.7 and 20.8 million, respectively, compared with 17.7 million in the United States). The projected 2030 figures for individuals with diabetes are 79.4 million in India, 42.3 million in China, and 30.3 million in the United States (1). In developing countries, the majority of people with diabetes are in the 45- to 64-year age range. In contrast, the majority in developed countries are over 64 years of age.
- T2DM was once considered to be a disease of adulthood, but it has recently been recognized with increased frequency in children and adolescents**, particularly within some ethnic groups such as Native Americans (2). Ten years ago, 3% of new-onset diabetes in adolescents was type 2; currently, 45% of cases are designated T2DM (3). The onset of diabetes in the second decade of life coincides with the physiological occurrence of pubertal insulin resistance. Up to 75% of young people diagnosed with T2DM have a first- or second-degree relative with the condition.
- Diabetes prevalence is higher in men than in women, but there are more women in total with diabetes.** T2DM, in contrast to T1DM, is notable for its close association with conditions such as hypertension, dyslipidemia, and obesity, which further raises the impact of T2DM on the health outcomes of affected individuals.
- In the United States, 95% of diabetes cases are T2DM, but T1DM has also shown increased incidence over recent years. The increase occurs largely in the youngest individuals (< 5 years) and those with moderate genetic susceptibility (4). A variety of environmental factors and the increasing incidence of childhood obesity are currently being studied as potential causes.

B. Spectrum of insulin resistance to T2DM

- There is a continuum between the early pathological features of disordered glucose metabolism and T2DM.

TABLE 45.2 Criteria for the Diagnosis of Diabetes and Prediabetes**Diabetes:**

- **HbA1c** $\geq 6.5\%$

or

- **Fasting plasma glucose** ≥ 126 mg/dL (7.0 mmol/L)

or

- **2-H plasma glucose** ≥ 200 mg/dL (11.1 mmol/L) in 75-g oral glucose tolerance test

or

- **Random plasma glucose** ≥ 200 mg/dL (11.1 mmol/L) with classic hyperglycemia signs/symptoms

In the absence of unequivocal hyperglycemia, results should be confirmed by a repeat test.

Prediabetes:

- **HbA1c** 5.7–6.4%

or

- **Fasting plasma glucose** 100–125 mg/dL (5.6–6.9 mmol/L) = impaired fasting glucose

or

- **2-H plasma glucose** 140–199 mg/dL (7.8–11.0 mmol/L) in 75-g oral glucose tolerance test = impaired glucose tolerance

From American Diabetes Association. Standards of Medical Care in Diabetes 2011. *Diabetes Care*. 2011;34(suppl 1):S11–S81.

- a. A diagnosis of diabetes can be made on the basis of a fasting blood glucose ≥ 126 mg/dL (7.0 mmol/L) or a 2-hour plasma glucose of ≥ 200 mg/dL (11.1 mmol/L) during a 75-g oral glucose tolerance test. A HbA1c $\geq 6.5\%$ has now been added to the ADA criteria for the diagnosis of diabetes. In the absence of unequivocal hyperglycemia, a positive result for any of these criteria should be confirmed on repeat testing. In the setting of classic hyperglycemic symptoms, a single random glucose ≥ 200 mg/dL is considered diagnostic (5). These diagnostic criteria are summarized in Table 45.2.
- b. It is now recognized that the microvascular and macrovascular complications of diabetes are not limited only to individuals meeting the diagnostic criteria for established diabetes. The progression from normal glucose tolerance to T2DM involves intermediate stages of impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), also collectively termed “prediabetes.” This pathological continuum arises from dysregulation of the balance between insulin sensitivity and insulin secretion.
- c. There is usually a long phase of asymptomatic pathology prior to the development of overt T2DM. Longitudinal studies suggest that insulin resistance onset occurs 10 to 20 years prior to the diagnosis of diabetes and is the best predictor of whether an individual will develop T2DM later. Insulin resistance places pressure on the pancreatic β -cells to augment secretion of insulin and, therefore, promotes β -cell dysfunction. Once the β -cell is unable to compensate sufficiently for the peripheral insulin resistance state, progression to T2DM will ensue. The underlying etiology of T2DM is complex, with both environmental and genetic predisposing factors promoting insulin resistance and β -cell dysfunction.

- d. The most notable epidemiological evidence regarding the impact of prediabetes states comes from the DECODE group. They have demonstrated that subjects without a diagnosis of diabetes have no threshold level of fasting or 2-hour postload glucose concentration above which the risk of all-cause or cardiovascular mortality death increased sharply. The relationship between 2-hour postload glucose and cardiovascular mortality was linear, with a continuum of risk extending into and below the prediabetes glucose range (6).
 - e. Current interpretations of data sets suggest that the cardiovascular effects of postprandial or postglucose challenge hyperglycemia are greater than those of IFG (7). During the prediabetes phase, the cardiovascular event rate is modestly increased. There is evidence for a higher mortality in individuals with IGT compared with those with IFG, which is independent of HbA1c or fasting blood glucose (8). The Emerging Risk Factors Collaboration found that individuals without a diagnosis of diabetes showed only a modest nonlinear correlation between fasting blood glucose and cardiovascular end points; postprandial glucose was not investigated.
 - f. There is evidence that the pathogenic effect of hyperglycemia on the endothelial cells already exists in the prediabetes stage.
2. The full transition from the early metabolic abnormalities of prediabetes to established diabetes probably occurs in about two-thirds of individuals.
- a. There is interest in determining **interventions that may decrease the likelihood of progression to diabetes** or reduce the future cardiovascular event rate once diabetes occurs. The Diabetes Prevention Program Research Group randomly assigned 3,234 participants without diabetes, but with elevated fasting and postload glucose concentrations, to placebo versus metformin (850 mg twice daily) versus a lifestyle modification program promoting exercise and weight loss (9). The incidence of diabetes over an average follow-up of 2.8 years was 11.0, 7.8, and 4.8 cases per 100 person-years in the placebo, metformin, and lifestyle groups, respectively. **The lifestyle intervention was significantly more successful in preventing diabetes than the metformin strategy.** Also of note is the STOP-NIDDM trial, which randomized individuals with IGT to acarbose (which primarily affects postprandial glycemia) or placebo (10). Patients in the acarbose group were observed to have a lower rate of diabetes diagnosis than those receiving placebo. Furthermore, a lower rate of cardiovascular disease and hypertension over a 3.3-year mean follow-up period was reported in the acarbose group (11).
- C. **Impact of diabetes on heart disease**
- 1. Both T1DM and T2DM confer significantly elevated risks of CAD, acute coronary syndromes, post–myocardial infarction (MI) complications, heart failure, and probably also sudden cardiac death. In addition, the incidences of peripheral arterial disease, stroke, and end-stage renal failure are elevated in individuals with diabetes. The cardiovascular complications of T2DM account for the majority of the socioeconomic burden of this chronic disease on both individuals and society.
 - a. **As many as 80% of individuals with diabetes will die from cardiovascular causes.** Per the Framingham Heart Study, the risk of CAD is doubled in men and tripled in women with diabetes, compared with age-matched subjects without diabetes.
 - b. In the modern era of drug-eluting stents and dual antiplatelet therapy, the mortality associated with CAD is falling overall. However, women with diabetes were observed to have a rise in CAD mortality in the period 1995 to 2003 (12).
 - c. More recently, the Emerging Risk Factors Collaboration undertook a large meta-analysis that demonstrated a twofold excess risk of outcomes such as coronary heart disease, coronary death, and nonfatal MI among individuals with established diabetes (13). They also found diabetes to be a third more strongly related to fatal than to nonfatal MI, possibly suggesting more severe manifestations of

coronary disease in those with diabetes. Hazard ratios (HRs) were particularly elevated for cardiovascular disease among individuals with diabetes who were female, younger, and non-smokers or had lower-than-average blood pressure.

- d. **Patients with diabetes present differently from those without diabetes and are much more likely to experience an acute coronary syndrome without chest pain, known as “silent ischemia.”**
 - e. Various angiographic trials have demonstrated that patients with **diabetes undergoing percutaneous coronary intervention (PCI) or coronary artery bypass surgery (CABG) tend to have significantly more severe CAD**, with a preponderance of multivessel disease and greater severity of lesions than those without diabetes. Despite the more severe plaque burden, diabetes correlates with lesser collateral vessel formation.
 - f. A particularly high risk is observed among individuals with T2DM following their first cardiovascular event. Indeed, there are multiple studies suggesting poorer outcomes following cardiovascular events, even with revascularization, for individuals with diabetes compared with those without. Cubbon et al. (14) reported that diabetes conferred a higher 30-day mortality after urgent PCI (9.4% patients with diabetes vs. 5.9% without diabetes, $p < 0.001$).
 - g. Post-MI complications and mortality in patients with diabetes correlate with post-MI ejection fraction and the presence of multivessel coronary disease. **Cardiogenic shock is more common and more severe in post-MI patients with diabetes.** The higher in-hospital mortality among the post-acute coronary syndrome (ACS) population with diabetes is largely related to the greater incidence of acute decompensated heart failure and to a lesser extent the increased risk of reinfarction and infarct extension.
 - h. The CAD mortality arising from T1DM has also been studied. Laing et al. reported a prospective study of 23,751 individuals with T1DM where subjects were followed for up to 29 years (15). As is typical of a T1DM cohort, the relatively young age correlated with a low event rate. However, their CAD risk was several times higher than that of a matched population without diabetes.
 - i. There is now sufficient literature to conclude that **chronic hyperglycemia per se, rather than the associated cardiovascular risk factors, has a pathogenic role in the development of vascular disease in diabetes.**
- D. Risk factors for CAD in patients with diabetes**
1. The risk factors that predispose individuals with diabetes to develop cardiovascular disease are the same as those that raise cardiovascular risks in those without diabetes. However, the prevalence of known major risk factors for CAD is generally amplified among persons with diabetes. Given the overall higher cardiovascular risk conferred, the benefits of tighter risk factor control may be greater in those with diabetes than those without. The potential gains of aspirin, attaining a normal body weight and nonsmoking status, tight blood pressure control, and aggressive lipid management in diabetes have been the subject of several recent trials.
 2. **a. Dyslipidemia**
 - (1) This is one of the most profound risk factors among individuals with diabetes. Diabetes is associated with small, dense low-density lipoprotein (LDL) particle composition, increased levels of apolipoprotein B and E, low levels of high-density lipoprotein (HDL) cholesterol, and high triglyceride (TG) levels. These lipid composition abnormalities cluster with insulin resistance and abdominal adiposity and appear to induce endothelial dysfunction and an increased susceptibility to thrombosis.
 - (2) Lipid-lowering therapy is now a cornerstone of T2DM management. In the Scandinavian Simvastatin Survival Study (4S), there was a 55% reduction in cardiovascular events among subjects with diabetes and a 25% reduction in the CARE trial. The National Cholesterol Education Program

(NCEP) considers diabetes a CAD equivalent in its Adult Treatment Panel III guidelines. Hence, a target of < 100 mg/dL—with an optional goal of < 70 mg/dL—is recommended (16). Statins are considered first-line agents to achieve these targets. Niacin may be of use in elevating HDL levels. Bile acid binding resins (along with thiazides, estrogens, and glucocorticoids) may increase TG levels and therefore should be avoided where possible.

b. Hypertriglyceridemia

- (1) **Elevated fasting TG levels** are characteristic of the lipid panel in diabetes and **constitute an independent cardiovascular risk factor**. Hypertriglyceridemia correlates with abdominal adiposity.
- (2) Fibrates have traditionally been considered an appropriate therapy to target hypertriglyceridemia and have often been added to statin therapy for this indication. The Helsinki Heart Study demonstrated the benefit of fibrates in a primary prevention trial to reduce cardiovascular end points (but not mortality), and the **VA HDL Intervention Trial (VA-HIT)** showed outcomes benefit in a secondary prevention setting. However, the lipid arm of the **ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial** did not demonstrate any benefit for subjects with T2DM in the addition of fenofibrate to simvastatin. The significant rhabdomyolysis risk with a fibrate and statin combination should also be considered.

c. Hypertension

- (1) **The prevalence of hypertension is increased in individuals with diabetes compared with those without.** The presence of an elevated blood pressure serves as at least as strong a risk factor for CAD as it does for individuals without diabetes.
- (2) **There are multiple large trials supporting the benefit of blood pressure lowering in subjects with diabetes.** In the UKPDS, lowering the blood pressure to a mean of 144/82 mm Hg (compared with 154/87 mm Hg) significantly reduced strokes, diabetes-related deaths, and heart failure, as well as microvascular complications. In that trial, there did not appear to be an outcome benefit between captopril and atenolol (17). However, several trials since have demonstrated the renal protective effects of angiotensin-converting enzyme (ACE) inhibitors (or angiotensin receptor antagonists) over alternate agents, which has firmly established them as the first-line antihypertensives in diabetes.

The **Hypertension Optimal Treatment (HOT) trial** demonstrated the benefit of a lower diastolic target. Among the 3,000 subjects with diabetes, but not in those without diabetes, the relative cardiovascular risk was significantly reduced in the ≤ 80 mm Hg group, compared with the ≤ 90 mm Hg group (18). Major guidelines suggest a target blood pressure in patients with diabetes of $< 130/80$ mm Hg. The ACCORD trial randomized subjects with diabetes to a target systolic blood pressure of < 120 mm Hg or < 140 mm Hg. The lower target group showed no difference in the primary cardiovascular outcomes end point but did have a significantly lower stroke rate; however, this was at the expense of significantly more adverse drug events and an increased risk of a creatinine rise of > 1.5 mg/dL (19). There is currently insufficient evidence to recommend ACE inhibitors in normotensive patients with diabetes without microalbuminuria.

d. Tobacco. There is evidence that smokers with diabetes have a markedly increased risk of MI and peripheral arterial disease. Lipid abnormalities and the development of atherosclerotic plaques appear to be promoted by smoking in the setting of diabetes.

e. Obesity

- (1) The prevalence of obesity has more than doubled in the United States since 1980. Obesity and overweight are typically defined in terms of

body mass index (BMI), with overweight being 25 to 30 kg/m², class I obesity 30 to 35 kg/m², class II obesity 35 to 40 kg/m², and class III obesity > 40 kg/m². Waist circumference and waist-to-hip ratio better reflect abdominal adiposity and are more reliable predictors of CAD outcomes than BMI (20). Obesity is an important determinant of cardiovascular health and is associated with widespread alterations in cardiac and vascular structure and function. It has been shown to be an independent risk factor for the development of cardiovascular disease. **T2DM correlates closely with obesity, especially central obesity.**

- (2) Caloric restriction, behavior modification, and increased physical activity form the basis of weight management programs. Unfortunately, sustained weight loss is difficult to achieve with these conservative measures. Several medications have been marketed for temporary assistance with weight loss.
 - (a) Sibutramine is a combined inhibitor of neuronal norepinephrine, serotonin, and, to a lesser degree, dopamine reuptake. It is a sympathomimetic and therefore increases heart rate and blood pressure, leading to concerns regarding its cardiovascular safety profile. It has recently been withdrawn from the market in multiple countries including the United States.
 - (b) Ephedrine and ephedra alkaloids ("ma huang") are sympathomimetic amines with a prolonged duration of action and increased peripheral effects. Due to safety concerns, ephedrine with or without caffeine and the ephedra alkaloids are not approved for treatment of obesity.
 - (c) Phentermine and diethylpropion are the only sympathomimetic drugs currently approved for the short-term treatment of obesity. Their use is not widespread.
 - (d) Orlistat is currently the only drug that is available for modulation of fat digestion. It inhibits pancreatic lipases, thus increasing the proportion of fat that is not completely hydrolyzed and is fecally excreted. The recommended prescription dose is 120 mg three times daily. A 60 mg over-the-counter version is available in some countries, including the United States. Major side effects include abdominal cramps, flatus, fecal incontinence, diarrhea, and oily stools; there is a rare association with severe liver injury.

Multiple trials have demonstrated a greater initial weight loss with orlistat, compared with placebo, and also slower weight regain in the longer term. In obese individuals with diabetes, orlistat not only promotes weight loss but also decreases A1c at 1 year in comparison with placebo (21).

- (e) Other drugs that may have effects in supporting weight loss include antidepressants such as fluoxetine, sertraline, bupropion; anti-epileptics such as topiramate and zonisamide; and diabetes medications including metformin and the glucagonlike peptide (GLP) analogs.
- (3) **There is growing evidence regarding the beneficial effects of significant weight loss achieved by bariatric surgery on glucose metabolism.** Bariatric surgery is generally restricted to individuals with BMI > 40 kg/m² or BMI 35 to 40 kg/m² with co-existing medical conditions such as diabetes, although the 2005 revision of the NIH consensus statement by the American Society for Bariatric Surgery expanded the indications to BMI 30 to 35 kg/m² with comorbidities.
 - (a) Bariatric surgery options include malabsorptive procedures such as the Roux-en-Y gastric bypass (currently accounting for the majority of bariatric operations in the United States) and restrictive procedures such as laparoscopic adjustable gastric bands and sleeve gastrectomy. The most recent data from the Longitudinal Assessment of Bariatric Surgery Consortium show a 30-day mortality rate of < 1% (22).

- (b) Weight loss post bariatric surgery is typically expressed in terms of “excess weight,” which refers to the difference between the actual and the ideal weights for an individual. Weight loss after malabsorptive bariatric surgery tends to reach a nadir at 12 to 18 months with an average of 70% excess body weight loss and a 35% decrease in BMI, with an approximate 10% weight regain in the following 10 years (23).
 - (c) A meta-analysis of 22,000 patients demonstrated that an average excess body weight loss of 61% was accompanied by significant improvements in T2DM, hypertension, dyslipidemia, and obstructive sleep apnea. Indeed, bariatric surgery has demonstrated an ability to completely reverse established diabetes in a large number of subjects. In the Swedish Obese Subjects Study (23), a prospective, nonrandomized, intervention trial of 4,047 obese subjects, 72% of individuals with diabetes who chose the bariatric surgery option showed reversal of their diabetes at 2 years, compared with 21% of those who followed a conservative weight loss regimen of diet and exercise. At 10 years follow-up, diabetes was reversed in 36% of the bariatric surgery group and 13% of the control group. In a smaller study of 165 obese patients with diabetes by Pories, 83% showed diabetes remission at a mean of 9.4 years (24). In the recent STAMPEDE trial, 150 patients with uncontrolled T2DM and a BMI between 27 and 43 kg/m² were randomized to intensive medical therapy alone, versus medical therapy plus Roux-en-Y gastric bypass or sleeve gastrectomy. The proportion of patients with HbA1c \leq 6.0% at 12 months was 12% in the medical therapy group, versus 42% in the gastric-bypass group ($p = 0.002$) and 37% in the sleeve-gastrectomy group ($p = 0.008$).
 - (d) There is growing evidence that there are both substantial modifications in the traditional CAD risk factors post bariatric surgery and that these risk modifications translate to a cardiovascular outcome benefit. The largest study of Framingham risk scores and actual cardiovascular events after gastric bypass involved 500 patients (without a control group) (25). At 1 year, the mean excess body weight loss was 68.7% \pm 22%. The diabetes prevalence fell from 28% to 6% ($p = 0.001$). The average 10-year absolute cardiovascular event risk, as estimated from the Framingham data, was 5.4% at baseline. This reduced to 2.7% at 1 year postsurgery ($p = 0.001$). The actual rate of cardiovascular events observed in this cohort postoperatively was only 1%.
3. Multifactorial risk factor interventions should be targeted in all patients with diabetes, regardless of whether this is a primary or a secondary prevention strategy.
- a. The Steno-2 trial randomized 160 patients with T2DM and microalbuminuria to intensive versus conventional therapy for a mean period of 7.8 years (26). The trial was designed to evaluate the effect on cardiovascular events of an intensified, targeted, multifactorial intervention comprising behavior modification and polypharmacologic therapy aimed at several modifiable risk factors in patients with T2DM.
 - b. The intensive management regimen included dietary fat restriction, 30 minutes of exercise three to five times per week, smoking cessation, ACE inhibitors or angiotensin receptor blocker administration irrespective of blood pressure, additional agents to target blood pressure $< 130/80$ mm Hg, 150 mg aspirin, stepwise glycemia management to target A1c $< 6.5\%$, statins for hyperlipidemia, and fibrates for isolated hypertriglyceridemia. The intensive group achieved significantly lower blood pressure, HbA1c, LDL, and TGs. There was an absolute risk reduction of 20% in cardiovascular events.
 - c. The subjects were then followed up for a further mean of 5.5 years, at which point the primary end point of all-cause mortality was assessed (27).

Significant differences in blood pressure, A1c, LDL, and TGs were absent by this later follow-up point. The primary end point at 13.3 years was time to all-cause death, and an absolute risk reduction of 20% was found. Even beyond the period of tight risk factor control, the Kaplan-Meier curves for the first cardiovascular event continued to diverge. During the mean 13.3-year follow-up period, the mortality rate among the conventional therapy subjects was 50%, a finding that highlights the poor overall outcomes in patients with diabetes who are not intensively managed.

- d. This study established that there were long-term benefits to aggressive multifaceted risk factor management, and that tight glycemic control and treatment with aspirin, antihypertensives, and lipid-lowering drugs appeared to be additive. Therefore, current society and national guidelines stress the importance of a broad approach to targeting multiple cardiovascular risk parameters. This body of evidence is much more firmly established than that regarding any benefit from tight glycemic control as a single approach to reducing cardiovascular risk.

E. Metabolic syndrome

The term “metabolic syndrome” describes the clustering of several of these cardiovascular risk factors in association with impaired glucose metabolism. There are slightly differing diagnostic criteria established by the WHO (28), the AHA and IDF (29), and the NCEP (30). The 2009 joint AHA/IDF criteria are summarized in Table 45.3. The value of the concept of the metabolic syndrome may lie in the emphasis it has placed on considering the patient as a whole and also the concept of abdominal adiposity being the more relevant predictor of CAD than BMI. However, several commentators have recently challenged the relevance of the metabolic syndrome, as it appears that accounting for the presence of the metabolic syndrome does not serve as a stronger predictor of cardiovascular risk than the individual component parameters (31).

F. Role in pathology of atherosclerosis

1. Diabetes accelerates the atherosclerosis process. Autopsy series have revealed more diffuse coronary involvement, greater severity of vessel stenosis, and more severe left main disease in persons with diabetes, compared with those without. Similarly, adverse coronary anatomy findings have been observed in autopsy studies of patients with a history of childhood onset of T1DM who died before the age of 40 years. The pathophysiology of atherosclerosis in diabetes remains incompletely understood but is thought to involve the hyperglycemia, lipid abnormalities, and

TABLE 45.3 Joint AHA and IDF Criteria for the Diagnosis of the Metabolic Syndrome

Metabolic syndrome

- **Waist circumference** in excess of population- and country-specific dimensions
- **Elevated triglycerides** ≥ 150 mg/dL (1.7 mmol/L), *or drug treatment for hypertriglyceridemia*
- **Low HDL** < 40 mg/dL (1.0 mmol/L) in males or < 50 mg/dL (1.3 mmol/L) in females, *or drug treatment for low HDL*
- **Elevated blood pressure** systolic ≥ 130 mm Hg and/or diastolic ≥ 85 mm Hg, *or antihypertensive drug treatment in a patient with diagnosis of hypertension*
- **Elevated fasting glucose** ≥ 100 mg/dL (5.6 mmol/L), *or drug treatment for hyperglycemia*

AHA, American Heart Association; HDL, high-density lipoprotein; IDF, International Diabetes Federation.

From Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome. A joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120:1640–1645.

dysfunctional endothelial and vascular smooth muscle function, coupled with a propensity for inflammation, thrombosis, and platelet activation.

2. It is recognized that the synthesis of nitric oxide (NO) by the vascular endothelium is reduced in subjects with diabetes. NO is among several key substances that maintain healthy endothelial function, which includes freedom from adhesion molecule activation, leukocyte diapedesis, platelet aggregation, and activation of thrombosis. However, the bioavailability of NO is adversely affected by hyperglycemia, high levels of free fatty acids, and insulin resistance. Current research reveals the impact of excessive oxidative stress (which can be induced by hyperglycemia, fatty acids, or insulin resistance) on NO production and also on the generation of advanced glycation end products, which are suspected to mediate various negative cellular effects in diabetes. Reactive oxygen species also activate protein kinase C with wide-ranging effects on cellular metabolism, including activation of the PI3K pathway, which has a role in mediating cell adhesion and migration. The ability of NO to act on vascular smooth muscle and cause vasodilation is reduced; endothelial cell dysfunction in diabetes is coupled with increased production of vasoconstrictors such as prostanooids and endothelin.

Another key pathogenic feature of atherosclerosis in diabetes is the PI3K- and nuclear factor κ B-stimulated alterations in adhesion molecule expression on the endothelial surface. This causes the endothelium to become more adherent to passing cells, and selectins on the surface of leukocytes attach to receptors such as ICAM-1 (intercellular adhesion molecule 1) and VCAM-1 (vascular cell adhesion molecule 1) and migrate into the intima. Here monocytes take on oxidized LDL and become macrophage foam cells, which are instrumental in the development of an atherosclerotic plaque. The tendency toward small, dense LDL particles in diabetes is another factor contributing toward atherosclerosis. Smooth muscle cell proliferation ensues, leading to deposition of collagen and other extracellular matrix proteins into the plaque.

Platelet function is also abnormal in diabetes, with overexpression of the glycoprotein IIb/IIIa receptor promoting inappropriate platelet adhesion and activation. Upregulation of multiple coagulation factors such as factor VII, thrombin, tissue factor, and plasminogen activator inhibitor-1 increases the tendency toward clotting, therefore contributing to the risk of thrombosis at the site of a plaque rupture or stent placement.

III. MICROVASCULAR TRIALS (as summarized in Table 45.4)

- A. The role of tight control of glycemia was firmly established in the 1990s with the publication of **two large trials demonstrating decreases in microvascular complications—primarily nephropathy and retinopathy—with lower glucose goals**.
 1. The Diabetes Control and Complications Trial (DCCT) recruited 1,441 patients with T1DM, of whom 726 had no retinopathy at baseline and 715 had mild retinopathy (32). Subjects were randomly assigned to an external insulin pump or three or more daily insulin injections to target a fasting glucose < 6 mmol/L. Conventional therapy had no glucose goals beyond those needed to prevent symptoms and comprised one or two daily injections of insulin. The two treatment groups were followed for a mean of 6.5 years between 1983 and 1993, with the mean HbA1c attained being 7.4% and 9.1%, respectively. In the primary prevention cohort (those without baseline retinopathy), intensive therapy reduced the adjusted mean risk of retinopathy development by 76%. With the two cohorts combined, intensive glucose control reduced the occurrence of microalbuminuria by 39%.
 2. The UK Prospective Diabetes Study (UKPDS) recruited 5,102 newly diagnosed T2DM patients from 1977 to 1991 with a median baseline HbA1c of 9.1% (33). The 4,209 patients who could not be controlled on diet alone were managed with differing therapies to determine if there were any specific advantages

TABLE 45.4 Characteristics of the Major Randomized Controlled Trials of Intensive Glucose Control in Type 2 Diabetes

	UKPDS 33	ACCORD	ADVANCE	VADT
Participants (n)	3,867	10,251	11,140	1,791
Diabetes duration (y)	0	10	7.9	11.5
Mean age (y)	53	62	66	60
History of CV disease (%)	Not reported	35	32	40
Duration of intervention (y)	10.0	3.5	5.0	5.6
Intensive group treatment	Sulfonylurea or insulin	Any oral drugs, insulin (91% rosiglitazone)	Gliclazide, other drugs including insulin	Glimepiride or metformin, plus rosiglitazone, or insulin
Standard group treatment	Diet	Any oral drugs, insulin (57% rosiglitazone)	Any oral drugs, insulin	Glimepiride or metformin, plus rosiglitazone, or insulin
Intensive group goal	FPG < 6.0 mmol/L	A1c < 6.0%	A1c ≤ 6.5%	1.5% absolute A1c reduction, cf. standard group
Standard group goal	FPG 6.1–15.0 mmol/L	A1c 7.0–7.9%	Local standards	Local standards
Baseline median A1c (%)	7.1	8.1	7.5	9.4
Achieved median A1c (%)	7.0 vs. 7.9	6.4 vs. 7.5	6.5 vs. 7.3 (mean)	6.9 vs. 8.4
Primary CV outcome	MI and sudden cardiac death	Nonfatal MI or stroke, or CV mortality	Nonfatal MI or stroke, or CV mortality	Nonfatal MI or stroke, CV mortality, heart failure, vascular surgery, inoperable CAD, amputation
Hazard ratio for primary outcome	16% risk reduction ($p = 0.052$)	0.90 (95% CI 0.78–1.04)	Macrovascular 0.94 (95% CI 0.84–1.06)	0.88 (95% CI 0.74–1.05)
Hazard ratio for death	0.87 ($p = 0.006$)	1.22 (95% CI 1.01–1.46)	0.93 (95% CI 0.83–1.06)	1.07 (95% CI 0.80–1.42)

ACCORD: Action to Control Cardiovascular Risk in Diabetes; ADVANCE: Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation; CAD: coronary artery disease; CI: confidence interval; CV: cardiovascular; FPG: fasting plasma glucose; MI: myocardial infarction; UKPDS: UK Prospective Diabetes Study; VADT: Veterans Affairs Diabetes Trial.

From Kelly TN, Bazzano LA, Fonseca VA, et al. Systematic review: glucose control and cardiovascular disease in type 2 diabetes. *Ann Intern Med*. 2009;151:394–403.

or disadvantages between glucose-lowering agents. A total of 342 obese subjects were allocated to the metformin group; of the remaining patients, 30% were randomized to conventional therapy and 70% to insulin or a sulfonylurea. The intensive group aimed for a fasting plasma glucose < 6 mmol/L. The median HbA1c achieved was 7.0% in the tight control group versus 7.9% in the conventional group. There was a significant 25% risk reduction (95% confidence interval [CI] 7% to 40%) in the end point of renal failure or death from renal failure, vitreous hemorrhage, or photocoagulation in the intensive control group.

In summary, the two large trials published in the 1990s, DCCT and UKPDS, showed significant improvements in microvascular outcomes with tighter glycemic control in T1DM or T2DM.

IV. MACROVASCULAR TRIALS

- A. Despite the convincing evidence for a reduction in microvascular complications, the relationship between glycemia and cardiovascular events remained unclear, with neither DCCT nor UKPDS showing a definitive advantage in terms of cardiovascular outcomes or mortality.
- B. The DCCT did not reveal a significant difference in macrovascular outcomes between the two treatment groups, but this relatively young cohort of T1DM patients would have been expected to have a low event rate. However, intensive glycemic control did reduce hyperlipidemia development.
- C. The UKPDS revealed a nonsignificant 16% risk reduction (95% CI 0% to 29%, $p = 0.052$) for fatal or nonfatal MI, or sudden death, with intensive management. In those subjects with $> 120\%$ ideal body weight who were allocated to the metformin strategy, there were significant benefits in terms of diabetes-related end points and all-cause mortality and a 39% risk reduction in MI. However, these results should be interpreted with caution due to the small numbers in the metformin subgroup.
- D. Two follow-up studies, and three new trials of intensive glucose control, sought to clarify the relationship between glucose control and cardiovascular events. Both the DCCT and the UKPDS cohorts were followed up for more than a decade from recruitment and their macrovascular outcomes assessed.
 1. The DCCT follow-up, known as EDIC (Epidemiology of Diabetes Interventions and Complications), monitored 93% of the original cohort until 2005, for a mean of 17 years of follow-up (34). Beyond 1993, DCCT subjects were placed onto whatever diabetes regimen their physician deemed appropriate, and so the distinction between standard and intensive management strategies was lost and the mean HbA1c's were the same. However, there was emergence of a macrovascular risk reduction in the group that had received the period of tight control earlier in the course of their T1DM; a 42% risk reduction for all cardiovascular events (95% CI 9 to 63, $p = 0.02$) was observed in this group.
 2. Similarly, the UKPDS subjects were invited for posttrial monitoring, with 3,277 patients attending annual clinics for a further 5 years (35). No attempts were made to maintain their previously assigned therapies, and indeed there was no persisting difference in A1c between groups at 1 year after initial trial conclusion. Data were then analyzed by original trial groupings. The sulfonylurea/insulin group showed a sustained decrease at 10 years for MI (15%, $p = 0.01$) and death from any cause (13%, $p = 0.007$). The metformin group showed a significant risk reduction in MI (33%, $p = 0.005$) and all-cause mortality (27%, $p = 0.002$).
 3. The DCCT/EDIC and UKPDS follow-up findings can be interpreted as showing "legacy" effects, whereby tighter management of glycemia early in the disease course confers cardiovascular and survival benefits more than a decade later. However, these potential delayed macrovascular benefits appear to be modest in comparison with long-term aggressive management of blood pressure and LDL.

- E. Three further large trials added additional information regarding the potential relationship between glycemic control and cardiovascular outcomes.
1. The Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) trial randomized 11,140 patients with T2DM to standard versus intensive glucose control (36). Intensive control was achieved with the use of gliclazide (a sulfonylurea) plus other agents as necessary to achieve a $HbA1c \leq 6.5\%$. After 5 years' median follow-up, the mean $A1c$ was 7.3% in the standard group and 6.5% in the intensive group. Insulin was prescribed for 40.5% and 24.1% of patients in the intensive group and the standard control group, respectively. There was a decrease in the incidence of microvascular events (primarily macroalbuminuria) but no significant effect of the type of glucose control on major macrovascular events (HR with intensive control 0.94), death from cardiovascular causes (HR 0.88), or death from any cause (HR 0.93). Of relevance, the nonglycemic risk factors were not fully optimized in many participants, with a mean systolic blood pressure of 135.5 ± 17.6 in the intensive glucose group and 137.9 ± 18.4 in the standard group and an LDL mean of around $120 \text{ mg/dL} \pm 20$ in both groups.
 2. The ACCORD trial also tested the effects of tight glucose control, recruiting a total of 10,251 T2DM patients who were randomized to a target $A1c$ of $< 6\%$ versus 7.0% to 7.9% (37). These participants were slightly younger than those studied in ADVANCE; they also tended to be heavier, had a higher median baseline $A1c$, and were much more likely to be using insulin prior to entry. ACCORD was discontinued at a mean follow-up of 3.5 years due to an increased risk of death in the intensive treatment arm. The primary outcome of nonfatal MI, nonfatal stroke, and cardiovascular mortality occurred in 352 patients in the intensive group versus 371 in the standard group (HR 0.90, 95% CI 0.78 to 1.04, $p = 0.16$). Hypoglycemia requiring medical attention and weight gain $> 10 \text{ kg}$ were both more common in the intensive therapy group. The finding of harm with a very aggressive $A1c$ target was surprising and could be related to adverse effects of hypoglycemia, especially in long-standing diabetes—19 of the 41 cardiovascular deaths were attributed to “unexpected or presumed cardiovascular disease,” and so could have been hypoglycemia-related. In addition, the average weight gain of 3.5 kg in the intensive control group (presumably drug-mediated) may have impacted on outcomes. It has also been noted that 91.2% of intensive therapy patients were receiving rosiglitazone, which was subsequently associated in other literature with an excess cardiovascular mortality, versus 57.2% of the standard therapy group.
 3. The VADT randomly assigned 1,791 predominantly male military veterans who had a suboptimal response to therapy for T2DM to receive either intensive or standard glucose control (38). The mean age was 60 years, 40% had already experienced a cardiovascular event, 52% were receiving insulin, and the mean baseline $HbA1c$ was 9.4%. This high-risk cohort was followed for a mean of 5.6 years, during which time the mean $A1c$ was 6.9% in the intensive group and 8.4% with standard care. However, there was no significant difference observed between the two groups in any component of the primary outcome or in all-cause mortality (HR 1.07, 95% CI 0.81 to 1.42; $p = 0.62$).
- F. The conclusion currently drawn from these studies is that there may be an early window in which tight glycemic control has the potential to achieve cardiovascular outcome benefits more than a decade later. However, ADVANCE, ACCORD, and VADT trials did not demonstrate any gains from a lower $HbA1c$ target over a follow-up period of 3.5 to 5.6 years. Additionally, there is a possibility that **very aggressive glucose lowering in patients with established diabetes may confer a survival disadvantage**.
- G. Recent meta-analyses incorporating the above trials have added additional information to this topic. The analyses by Turnbull et al. (39) and Kelly et al. (40) reached

similar conclusions, with pooled data showing a reduced risk of major cardiovascular events in the group with intensive glucose control compared with less aggressive control. However, in both cases, the risk reduction was small: a 9% risk reduction (HR 0.91, 95% CI 0.84 to 0.99) in the study of Turnbull and a relative risk of cardiovascular disease of 0.9 (95% CI 0.83 to 0.98) in the study of Kelly. Both concluded that cardiovascular mortality was unchanged between the two management strategies. Intensive glucose control was also highlighted as conferring at least a twofold risk for severe hypoglycemia in both papers. Both groups also found a small risk reduction regarding MI—a 15% reduction in fatal and nonfatal MI in the study of Turnbull and a 16% reduction of nonfatal MI risk in the study of Kelly. Turnbull et al. described a subgroup of patients who did not appear to benefit from more intensive control: individuals with a history of macrovascular disease existing prior to randomization.

Another meta-analysis, incorporating similar trials as the Turnbull and Kelly analyses, reached a slightly different conclusion. Ray et al. determined that intensive glucose lowering resulted in a significant reduction in nonfatal MI and in all coronary heart disease events. Cardiovascular mortality was not reported; all-cause mortality was equivalent in the pooled standard and intensive treatment groups (41).

- H. The 2009 ACC/AHA Scientific Statement supports a goal HbA1c of $\leq 7\%$, with acknowledgment of the benefits of tight control in terms of microvascular disease, but recognizes the paucity of evidence for a cardiovascular benefit (42).** Based on the currently available literature, individuals with diabetes cannot be confidently advised that stricter glucose control will reduce their likelihood of future cardiovascular events or mortality.

V. DIABETES PHARMACOTHERAPY

- A.** The spectrum of medications available to manage diabetes has expanded greatly over recent years. There has been increasing recognition that there may be significant differences between the cardiovascular impact of the various medications, even if the glycemic effects are equivalent.
- 1. Insulin** is available in short-, medium-, and long-acting preparations, with synthetic human insulin and analogs of human insulin differing in their rates of absorption and durations of action. Mixtures of rapid short-acting and intermediate-acting insulin are also commonly used. Recombinant human insulin is synthesized using *Escherichia coli* bacteria, and subtle variations in the amino acid chain deter the insulin molecules from forming aggregates, thus creating a faster-onset, shorter-acting drug than regular insulin.
- The different recombinant rapid-acting insulins—lispro, aspart, and glulisine—each have differing amino acid substitutions. All three can be injected subcutaneously to prevent postprandial glucose elevations, for rapid correction of elevated glucoses, and in insulin pumps. The onset of action is 15 minutes, with peak effect around 1 hour and a duration of action around 3 to 4 hours. An inhaled short-acting insulin was marketed briefly, but has now been withdrawn due to limited patient uptake.
 - Regular insulin is designated as a short-acting preparation. It has onset of action within 30 to 60 minutes, a peak time of 2 to 4 hours, and a duration of action around 6 to 8 hours. It can be used in intravenous infusions, as well as subcutaneously.
 - Neutral protamine Hagedorn (NPH) is an intermediate-acting insulin. Its time to onset is 1 to 3 hours, and the total duration of action is 12 to 16 hours. It can be injected either once daily at bedtime to lower fasting glucose levels (typically in individuals on oral hypoglycemics who are above A1c target) or as a twice-daily basal medication in combination with a shorter-acting prandial insulin. This latter approach is known as a basal-bolus regimen

and is widely used to achieve tight glucose control. In the basal-bolus regimen, a twice-daily intermediate-acting insulin, or a once-daily long-acting insulin, provides basal coverage and controls the fasting glucose levels. The three prandial insulin doses, administered just before mealtimes, cover the ingested carbohydrates and so limit postprandial glucose elevation. This is considered to be the most “physiologic” method of insulin administration, as it simulates the insulin-release patterns of the β -cells.

- d. Glargine and detemir are the available long-acting agents, usually injected at night, and show minimal peaking. Glargine has a 24-hour profile of action, whereas detemir is more variable at 6 to 24 hours.
2. **Insulin pumps** are devices that can be programmed to release a continuous infusion of insulin into the subcutaneous tissue. An abdominal infusion site is the usual location, and the catheter should be changed every 2 to 3 days. These pumps are generally used in patients with T1DM and are most suited to knowledgeable and motivated individuals. They have been demonstrated to achieve greater success with target A1c levels and reduce the number of severe hypoglycemic episodes, compared with traditional subcutaneous insulin injections. **A newer innovation is the subcutaneous continuous glucose-monitoring system that detects glucose levels in the interstitium of subcutaneous tissue.** The real-time display of glucose levels can assist patients in anticipating insulin requirements and avoiding severe hypoglycemia. The currently marketed devices are each limited to a few days of continuous wear. Closed-loop systems that consist of both a subcutaneous continuous glucose sensor and an insulin pump are in development.

Insulin can cause weight gain and carries a risk of severe hypoglycemia. The hypoglycemic risk is increased in patients with renal and/or hepatic dysfunction, as the liver and kidneys are responsible for the majority of gluconeogenesis and glycogenolysis; in addition, insulin is renal excreted. The associated weight gain and hypoglycemia raised questions when the ACCORD trial revealed higher mortality in the intense therapy arm, where 77% of subjects were using insulin (vs. 55% in the standard care arm). The recent Euro Heart study also suggested harm related to insulin use. Insulin-treated patients with diabetes had an adjusted 1-year HR for mortality of 2.23 (95% CI 1.24 to 4.03, $p = 0.006$) and for cardiovascular events of 1.27 (95% CI 0.85 to 1.87, $p = 0.230$) compared with those taking oral hypoglycemic agents (predominantly sulfonylurea, metformin, or a combination of the two) (43). However, this study was nonrandomized and the choice to prescribe insulin was made by the treating physicians.

- a. **Metformin** addresses glycemia by several mechanisms: it reduces hepatic gluconeogenesis by inhibiting glucose-6-phosphate dehydrogenase and works as a peripheral insulin sensitizer, with promotion of insulin-induced glucose movement into skeletal myocytes and adipocytes. As it does not stimulate insulin release, there is minimal hypoglycemic risk. This drug is considered first line in overweight patients with T2DM and is not associated with the weight gain that is encountered with insulin and the sulfonylureas. Metformin's insulin-sensitizing mechanisms have also found a role in the treatment of metabolic syndrome, polycystic ovarian syndrome, and nonalcoholic fatty liver disease, each of which is associated with insulin resistance. There is evidence for improvements in lipid profiles with metformin use. Metformin is contraindicated with impaired renal function (creatinine > 1.5 mg/dL in males and > 1.3 mg/dL in females is often quoted as the threshold) and also decompensated heart failure, where the risk of lactic acidosis may be elevated. Lactic acidosis, which can arise in the setting of reduced renal lactate clearance coupled with insufficient uptake of lactate into the liver because of gluconeogenesis inhibition, is considered to be rare. However, **it is standard of care to discontinue metformin**

during periods of renal impairment or inpatient heart failure treatment and for 24 hours before and 48 hours after injection of iodinated contrast agents. The majority of the reported side effects are gastrointestinal and can include diarrhea, nausea, early satiety, and abdominal pain.

- b. **Sulfonylureas** are **insulin-stimulating oral agents**, with action on the adenosine triphosphate (ATP)-sensitive potassium channel found on the pancreatic β -cell. Binding of a sulfonylurea causes a decrease in potassium efflux through the K_{ATP}^+ channel, inducing membrane depolarization that leads to calcium influx into the β -cell. Insulin release from secretory granules results. The main side effect is hypoglycemia; weight gain can also be a complication. Questions have also been raised regarding their potential to inhibit ischemic preconditioning via blockade of myocardial K_{ATP}^+ channels. The commonly used second-generation sulfonylureas, such as glipizide, glimepiride, and glyburide (also known as glibenclamide outside the United States), are largely metabolized by the liver and excreted renally.
- c. **Thiazolidinediones** are a newer class of drugs that have attracted much controversy with regard to their effects on the heart. The two agents developed in this class, **rosiglitazone** and **pioglitazone**, **act by increasing insulin sensitivity in target peripheral tissues**. This is achieved via activation of the peroxisome proliferator-activated receptor (PPAR)- γ nuclear receptor in myocytes and adipocytes, encouraging insulin-stimulated glucose transport into the cell. Pioglitazone also acts as a partial agonist of the PPAR- α receptor, which is believed to be the reason for increased HDL and decreased LDL and TGs observed with this drug.

Peripheral edema is a noted side effect; hence, this class of drugs should **not** be used in patients with NYHA class III–IV heart failure due to concerns for sodium and water retention and possible precipitation of heart failure decompensation. Weight gain, by expansion of subcutaneous adipose tissues, is also an associated complication.

There is some evidence, mostly using surrogate outcomes such as carotid intimal thickness and progression of coronary atherosclerosis by intravascular ultrasound, for a deterrent effect on atherosclerosis by pioglitazone in comparison with a sulfonylurea (44, 45). Analysis of a database including 16,390 clinical trial participants demonstrated that pioglitazone is associated with a significantly lower risk of death, MI, or stroke among a diverse population of patients with diabetes (46). However, the risk of heart failure was increased with pioglitazone, although without an associated increase in mortality. Conversely, rosiglitazone has been associated with an excess risk of MI and cardiovascular mortality in a meta-analysis (47). This led to the subsequent publication of the RECORD trial, which demonstrated overall noninferiority for a combination of metformin and sulfonylurea, but an increased risk of heart failure hospital admission or death with rosiglitazone (48).

- (a) **Meglitinides**, such as repaglinide and nateglinide, are relatively short-acting oral insulin secretagogues. They are taken just prior to a meal and help to lower postprandial glucose levels. Due to their short duration of action, meglitinides are useful in the elderly and individuals with erratic eating habits.
- (b) **Alpha-glucosidase inhibitors** such as acarbose and miglitol delay the absorption of complex carbohydrates via their action on the glycosidase enzymes in the brush border of the small intestine. They are generally used as an adjunctive therapy and can be useful in controlling postprandial glycemia. As described above, the STOP-NIDDM trial suggested a role for acarbose in reducing the progression of IGT to diabetes (11). The major side effects are flatulence and abdominal pain.

- (c) **Amylin** is also an adjunctive agent and can be combined with prandial insulin therapy in T1DM or T2DM patients not meeting glucose targets. Pramlintide is a synthetic version of endogenous amylin, which is synthesized by β -cells and secreted with insulin in response to a carbohydrate load. The major effects appear to be inhibition of gastric emptying and suppression of glucagon release. Insulin doses should be reduced on initiation of pramlintide injections to avoid potential hypoglycemia. This agent may assist in reducing body weight.
- (d) **Incretins** are a new class of agents for T2DM and include the GLP-1 and glucose-dependent insulintropic peptide (GIP). The incretin hormones stimulate β -cell proliferation in animal models and are found at lower-than-normal levels in patients with T2DM. The active form of GLP-1 is the amide GLP-1(7-36), which is secreted by entero-endocrine L cells of the ileum and colon in response to a carbohydrate load. Exenatide is a synthetic GLP-1 analog that is subcutaneously injected twice daily. It works by potentiating insulin secretion, decreasing postprandial glucagon, delaying gastric emptying, and promoting weight loss. Liraglutide works in a manner similar to exenatide but has a longer half-life and is dosed once daily. Side effects include diarrhea and vomiting, and hypoglycemia is also a concern.
- (e) **Dipeptidyl peptidase-4 (DPP-4) inhibitors** work by deterring the DPP-4-mediated degradation of GLP-1 and GIP into inactive metabolites. The first DPP-4 inhibitor to be marketed was the once-daily oral agent sitagliptin, with saxagliptin and vildagliptin (not approved in the United States) following since. There have been postmarketing concerns regarding pancreatitis and suggestions that inhibition of DPP-4 could promote carcinogenesis. DPP-4 inhibitors are weight neutral and carry a low risk of hypoglycemia; both liraglutide and exenatide have demonstrated the ability to reduce systolic blood pressure. Liraglutide also has a positive effect on the lipid profile and cardiovascular risk biomarkers.

Hence, the GLP-1 analogs and DPP-4 inhibitors have attracted significant recent attention regarding the possibility of favorable cardiovascular effects. GLP-1 receptors are known to exist on cardiomyocytes, and animal models of heart failure have shown positive responses to GLP-1. Improvements in left ventricular ejection fraction were reported in 10 patients who received a 72-hour GLP-1 infusion post-MI with successful primary angioplasty, when compared with 11 controls (49). Sokos et al. also reported significant improvements associated with a GLP-1 infusion in advanced heart failure patients (50). Of the 18 participants in NYHA class III–IV failure, 11 received a 10-week subcutaneous infusion with an escalating dose of GLP-1 and 7 received a placebo infusion. Significant improvements in the GLP-1 group were reported for several end points including left ventricular ejection fraction, oxygen consumption, the 6-minute walk test, quality of life, NYHA class, and B-type natriuretic peptide levels. However, neither of these pilot studies was randomized.

- B. With the host of contrasting mechanisms described, it is clear that the various medications for diabetes cannot be expected to have equivalent effects on the cardiovascular system and future cardiovascular events, irrespective of any similarities in the degree of glucose lowering. The potentially negative cardiovascular effects of insulin and the sulfonylureas are of particular interest for further investigation. BARI-2D aimed to shed light on this uncertainty, but did not reveal a cardiovascular outcome difference between individuals randomized to an insulin provision therapy (insulin or sulfonylurea) versus insulin sensitization (metformin or thiazolidinedione) over a mean of

- 5.3 years (51). However, the extensive use of rosiglitazone and a relatively high cross-over rate between the randomized groups confounded the interpretation of this trial.
- C. It is hoped that the next generation of large clinical trials addressing the relationship between glycemic control and cardiovascular outcomes will be able to tease apart the relative effects of the major drug classes on the heart. This may require a shift in focus away from HbA1c. As described above, postprandial glucose may be a useful parameter to follow in future cohorts.
- D. A related area of investigation has been the implementation of intensive glucose control regimens in the period immediately after an acute coronary syndrome.
1. The use of insulin in the setting of an acute MI was first described in the 1960s, with the goal of facilitating potassium flux in the ischemic myocardium. After decades of investigation, the combination of intravenous glucose, high-dose insulin, and potassium ("GIK" therapy) was concluded to offer no benefit in the setting of ST-segment elevation myocardial infarction (STEMI) and may have caused harm in some studies (52). Hence, this practice has been abandoned and should be distinguished from trials of intensive intravenous insulin therapy for tight glucose control post-MI.
 2. The first DIGAMI study actually used a GIK protocol and infused insulin at 5 units/h with intravenous glucose to achieve glucose in the 126 to 198 mmol/dL range. Therefore, it was not a study of tight glucose control, although it has often been misinterpreted as such. The DIGAMI study did, however, raise interest in post-MI glucose control by suggesting that a 24-hour insulin-glucose infusion followed by intensive subcutaneous insulin in patients with diabetes could improve long-term survival post-MI (53). The mortality benefit seen at 1 year continued out to 3.5 years, with an absolute mortality reduction of 11%. The effect was most apparent in patients who had not previously received insulin treatment and who were at a low cardiovascular risk.
 3. The subsequent DIGAMI-2 trial employed three acute MI glucose management strategies: acute insulin-glucose infusion followed by insulin-based long-term glucose control versus insulin-glucose infusion followed by standard glucose control versus routine metabolic management according to local practice (54). In the first two groups, the objective was to decrease the plasma glucose as rapidly as possible and maintain a level between 126 and 180 mg/dL. This trial did not reproduce the benefits seen in DIGAMI-1, with no differences seen in mortality or nonfatal re-infarctions between the three groups. As a result, guidelines currently recommend a more conservative target of < 180 mg/dL in the post-ACS phase.
 4. This more lenient approach was supported by the NICE-SUGAR trial, which randomized 6,104 patients to intensive glucose control (target blood glucose range of 81 to 108 mg/dL) or conventional glucose control (target < 180 mg/dL) (55). The intensive group showed a higher odds ratio (OR) for death of 1.14 (95% CI 1.02 to 1.28; $p = 0.02$). This was despite the incidence of hypoglycemia in the intensive control group (6.8%) being the lowest of all the post-MI trials published.
 5. HEART2D sought to test the approach of tight postprandial hyperglycemia control in patients enrolled within 21 days of a hospital admission for acute MI (56). It showed no difference between a prandial insulin therapy arm and a basal insulin arm over a mean follow-up of 963 days, but the study was hampered by a low event rate, short follow-up period, and only minimal differences in glycemia achieved between the two groups.
- E. **Novel and future diabetes therapies** offer new potential strategies to pursue normalization of glycemia. Islet cell transplantation, delivered via a catheter into the portal vein, is currently under investigation. Whole pancreas transplantation is occasionally performed, usually in the setting of a patient requiring renal transplant who is already receiving immunosuppressive medications. T1DM is caused by T-cell-mediated β -cell destruction. There are preliminary animal data that autoreactive T cells may be removed from the circulation using stem cells transduced

to express major histocompatibility complex class II β chains. Stem cells are also a potential source for regeneration of pancreatic β -cells. However, significant challenges include preventing autoimmune destruction of regenerated β -cells and inducing physiologic insulin release in these cells.

VI. REVASCULARIZATION IN PATIENTS WITH DIABETES

A. The cardiovascular management of patients with diabetes incorporates not only careful consideration of medical regimens but also review of the available literature with regard to revascularization strategies. There have been many advances in evidence-based management of obstructive coronary lesions over recent decades, and many of the trials have identified strategies that confer particular benefit in individuals with diabetes.

1. **CABG versus PCI.** A series of landmark trials in patients with obstructive CAD have defined current practice with regard to the decision between CABG and PCI. The finding in 1997 that **the BARI subgroup with diabetes had a significant survival benefit in favor of CABG heralded the onset of specific coronary strategies for patients with diabetes.** The subgroup was not prespecified, but the survival benefit was considerable: in subjects receiving insulin or oral agents for diabetes (347 of the total cohort of 1,829), those randomized to CABG had a 80.6% 5-year survival, whereas balloon angioplasty was associated with 65.5% survival (57). This was in the interventional era prior to coronary stenting, and the explanation for the poor PCI outcomes in BARI subjects with diabetes is a presumed high rate of vessel restenosis. In addition, patients with diabetes tend to have more diffuse CAD, and lesions distant from the angioplasty site are left unprotected by a PCI strategy.

2. **CABG versus PCI with bare metal stents (BMSs) and glycoprotein IIb/IIIa inhibitors.** The widespread adoption of coronary stenting—at this stage with BMS—was successful in reducing restenosis rates. Sustained angiographic coronary patency also correlated with superior survival outcomes, symptom scores, and improved regional left ventricular systolic function. The randomized Arterial Revascularization Therapy Study (ARTS) of CABG versus PCI in multivessel disease showed equivalence of major outcomes for CABG and PCI strategies, with the caveat that the incidence of repeat revascularization was higher in the PCI group (58).

This trial was also notable for its diabetes subgroup results; **there was a benefit in terms of 1-year repeat revascularization and major cardiovascular events in patients with diabetes who underwent CABG, as compared with stenting.** Other studies of this era, including the Stent or Surgery (SOS) trial published in 2002 (59), demonstrated superiority of CABG over PCI in patients with multivessel disease in general, but these were performed prior to routine use of thienopyridines and glycoprotein IIb/IIIa inhibitors. The addition of a platelet glycoprotein IIb/IIIa inhibitor appears to be particularly beneficial for patients with diabetes presenting with an ACS. A meta-analysis by Roffi et al. involving 6,458 patients with diabetes and non-ST-segment elevation ACS showed a significant reduction in the aggregate 30-day mortality (OR 0.74, 95% CI 0.59 to 0.92) with use of a glycoprotein IIb/IIIa inhibitor (60). Although not based on a randomized assessment, this survival advantage appeared to be particularly marked in patients who underwent PCI during the hospitalization.

3. **CABG versus drug-eluting stents (DESs).** DESs offer a further deterrent to vessel restenosis, although at the expense of an early in-stent thrombosis risk, particularly if antiplatelet medications are insufficient or ineffective. These stents deliver an antiproliferative drug locally to inhibit neointimal hyperplasia and improve target lesion patency. They have been clearly demonstrated to reduce angiographic restenosis rates, although there has been less of an impact on cardiovascular outcomes and mortality.

A 2006 meta-analysis of 12 studies by Kumbhani et al., including 1,902 patients with diabetes treated with either a DES ($n = 1,089$) or a BMS ($n = 813$), demonstrated an association between DESs and significant risk reductions in major adverse cardiac events (MACE), target lesion revascularization, and in-stent restenosis (with the reductions in MACE being primarily driven by the significant reductions in revascularization) (61). Also of note was an analysis comparing the relative risk of in-segment restenosis between the two types of DESs, which found a nonsignificant benefit favoring sirolimus-eluting stents versus paclitaxel-eluting stents (PESs).

Although there appears to be a dramatic restenosis reduction with the use of DESs compared with BMSs, patients with diabetes still encounter a higher rate of cardiovascular events post-PCI than those without diabetes. The comparative effectiveness of PESs or sirolimus-eluting stents in diabetes remains controversial. Increases in late stent thrombosis or restenosis, which are particularly likely in patients with diabetes and renal failure or complex lesions, need to be considered.

The SYNTAX trial investigated the strategies of PCI with PES versus CABG in patients with triple-vessel or left main disease; approximately 26% of SYNTAX participants had diabetes (62). An evaluation of the 452 SYNTAX subjects with diabetes, 40% of whom received insulin, showed that mortality was significantly higher among subjects with diabetes compared with those without, regardless of the revascularization strategy (63). At 1 year, the only outcome difference between PCI and CABG in patients with diabetes was the excess of repeat revascularization in the PCI arm. **Patients with diabetes had significantly increased repeat revascularization rates compared with those without diabetes when treated with PES, but not after CABG.** The CARDia trial was underpowered, but reached a similar conclusion. Stroke was nonsignificantly higher in the SYNTAX CABG arm. Further information on the relative merits of CABG and PCI in patients with diabetes and multivessel coronary disease is expected from the ongoing FREEDOM trial.

4. **Current antiplatelet strategies.** Antiplatelet requirements post-PCI do not differ between patients with or without diabetes. However, given the higher risks of target lesion revascularization and in-stent restenosis in those with diabetes, it can be expected that patients with diabetes have the most to lose from insufficient or ineffective antiplatelet therapy. Current recommendations are that all patients with coronary stents remain on daily aspirin lifelong. A thienopyridine should be taken for a very minimum of a month post-BMS placement; patients who receive a DES should take a thienopyridine uninterrupted for at least 12 months. The recent introduction of prasugrel has relevance to individuals with diabetes. TRITON-TIMI 38 enrolled intermediate-risk/high-risk ACS patients and STEMI patients who underwent PCI (64). Participants were randomized to prasugrel 60 mg load and 10 mg daily maintenance versus 300 mg load and 75 mg daily clopidogrel. The primary composite end point was significantly reduced with prasugrel in patients without diabetes (HR 0.86) and even more significantly reduced in those with diabetes (HR 0.70).
5. **CABG outcomes. Bypass conduit attrition rates are known to be higher in patients with diabetes.** As in patients without diabetes, the use of the internal mammary arteries (IMAs) offers higher long-term patency (in the region of 90% at 10 years) compared with reversed saphenous veins (long-term patency varying between 40% and 75%). Therefore, IMAs are particularly attractive in patients with diabetes, although the practice of using bilateral IMA grafts is controversial due to the potential for sternal wound infections. In addition to wound infections, patients with diabetes have an elevated risk of perioperative stroke with CABG surgery, with an OR of 1.4 (95% CI 1.2 to 1.8) for stroke (65). PCI does not carry an additional stroke risk for patients with diabetes and, therefore, may be the preferable option in patients with diabetes who have multivessel disease

and a preserved left ventricular ejection fraction and coronary lesions amenable to stenting. There are various measures such as preoperative noninvasive carotid artery assessment and modifications of the cross-clamp technique that can help to minimize peri-CABG stroke rates in high-risk patients.

6. **Revascularization versus optimal medical therapy.** The COURAGE trial raised questions regarding the relative merits of a purely medical versus medical and PCI strategy in patients with obstructive CAD and stable symptoms (66). This somewhat controversial study concluded that PCI added to optimal medical therapy did not reduce the primary composite end point of death and nonfatal MI or reduce major cardiovascular events over a 2.5- to 7.0-year period. A third of the participants had diabetes. The 1,605 patients with diabetes enrolled in the PCI versus optimal medical therapy stratum of BARI-2D did not show any difference in cardiovascular outcomes (51). However, both of these trials randomized patients after an initial angiogram that defined anatomy, and the decision to enroll in the PCI arm of BARI-2D (as opposed to the CABG arm) was made once anatomy was known and at the discretion of the investigators.
7. **Screening asymptomatic patients with diabetes for CAD.** Given the elevated risk of CAD in patients with diabetes, investigators have attempted to determine whether identification of asymptomatic CAD can improve future outcomes for patients with diabetes. The Detection of Ischemia in Asymptomatic Diabetes (DIAD) study used a nuclear cardiac stress imaging protocol to identify patients likely to have CAD (67). At 5 years, there was no difference in nonfatal MI or mortality between the nuclear screening and standard care groups. However, the screening arm was notable for a very low rate of significant ischemia detection, and there was a very successful protocol of optimal medication therapy among trial participants.
8. **Screening for diabetes in patients with cardiovascular disease or risk factors.** Given the degree of excess cardiac morbidity and mortality attributable to diabetes, and the proposed early window for tight glucose control with potential to impact on later cardiovascular risk, there is an argument for asymptomatic screening of high-risk patients for diabetes. **With the ease of diagnosis by HbA1c criteria and long asymptomatic prediabetes phase, T2DM meets WHO thresholds for a condition where screening may be appropriate.** However, it remains unproven as to whether early identification and aggressive management of diabetes has the ability to attenuate future cardiovascular risk. ADDITION-Europe sought to clarify this question with a cluster-randomized trial that assigned subjects to standard care versus an intense multifactorial management protocol (68). This study was not able to demonstrate a significant cardiovascular outcome benefit for early detection and management of diabetes at 5.3 years and was hampered by a low event rate and a smaller-than-expected difference in risk factor management between the two groups.

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Heart Disease in Women

I. INTRODUCTION. Cardiovascular disease (CVD) is by far the leading cause of death of women in the United States and most developed countries, accounting for almost 39% of all female deaths in the United States. In 2007, CVD caused 421,918 deaths in women in the United States, approximately 1 per minute, **more than those claimed by cancer, chronic lower respiratory disease, Alzheimer disease, and accidents combined**. Despite aggressive campaigns by the American Heart Association (AHA) and other organizations, only 54% of the women surveyed in 2009 spontaneously listed coronary heart disease (CHD) as a woman's leading cause of death, and only 13% of the women surveyed identified CHD as a risk for them personally. Minority women are even less aware of their cardiovascular (CV) risk, which is higher than for age-matched white women.

Some important gender-related differences exist in the presentation and outcome of CVD. In a national registry of over 300,000 patients (40% women) admitted with acute myocardial infarction (MI) between 1994 and 1998, female patients were found to be older compared with males (approximately 72 years vs. 66 years, respectively). Women also had higher in-hospital mortality compared with men (17% vs. 12%). Risk of death is particularly high in younger women, more than twice that of men in the under-50 age group, and also in women who presented with ST-elevation myocardial infarction (STEMI). These differences highlight an urgent need to better understand and treat heart diseases in women. This chapter summarizes current understanding of the gender-specific features of CVD based on large-scale clinical trials and existing and emerging molecular science.

II. GENDER DIFFERENCES IN PATHOPHYSIOLOGY. Briefly, coronary artery disease (CAD) begins with **nascent atheroma**, the coalescence of small lipoprotein particles within the arterial intima. Over time, these lipoprotein particles become oxidized, inducing local cytokine elaboration. These inflammatory cytokines cause the increased expression of adhesion molecules for leukocytes, leading to leukocyte attraction and migration into the intimal layer. Blood monocytes become macrophages upon entering the intima and express scavenger receptors on their surface, owing to their interaction with certain cytokines present locally. These scavenger receptors promote the uptake of modified lipoprotein particles, leading to the formation of **foam cells**. Foam cells further elaborate inflammatory and attractant cytokines and other effector molecules. In response, smooth muscle cells migrate into the intima from the media, where they proliferate and form fatty streaks. Smooth muscle cell proliferation and extracellular matrix accumulation lead to the progression from a **fatty streak** to a **fibrofatty plaque**. Later stages are characterized by calcification and fibrosis, occasionally with smooth muscle cell death. This creates an acellular fibrous cap surrounding a lipid-rich core.

The process of atherosclerosis progresses slowly, and patients often remain unaware and asymptomatic for many years. This is likely attributable to the capacity of the arteries to remodel—expanding outwardly as the intima expands, thereby preventing plaque encroachment on the lumen of the vessel. However, at some point the plaque

burden exceeds the ability of the vessel to remodel, and narrowing of the lumen begins. Eventually, if unimpeded, atherosclerosis will progress until the degree of luminal narrowing impedes blood flow. Initially, this luminal narrowing is apparent mostly under the conditions of stress, where arterial oxygen supply is unable to meet demand. Once this occurs, the patient begins to develop symptoms, typically stable angina.

In some cases, however, the first manifestation of the underlying CAD is MI, unstable angina, or sudden death. In these instances, the underlying stenosis is usually < 50% of the lumen diameter. The inciting event leading to symptoms in these cases is either physical disruption of the fibrous cap of the plaque or superficial erosion of the intima. Either setting exposes the underlying lipid-rich core to blood components and initiates thrombosis (see Chapters 1 and 2 for more detailed discussions). Women, **especially younger women, are twice as likely to have plaque erosion as the underlying cause of MI**, whereas men and older women more often have plaque rupture. Compared to men, whose plaques tend to be more dense fibrous, women also tend to have more cellular fibrous plaques.

There appears to be other gender-based differences in the atherosclerotic process. Hormones have also been proven to influence many of the underlying pathophysiologic processes, including vasoreactivity, thrombosis and inflammation. Women have smaller coronary arteries than men and, interestingly, women taking androgens have much larger coronary arteries than their age-matched controls. For years it was noted that premenopausal women appeared to be protected from CAD and estrogen emerged as the most likely reason. A recent animal study suggests that estrogen appears to decrease oxidative stress via upregulation of the production of prostacyclin PGI₂, a molecule known to retard the progression of atherosclerosis. The full spectrum of sex hormone effects on the heart and vascular system has yet to be fully determined. In addition, there have been genetic links to the development of CAD that are noted to vary according to gender, with different single-nucleotide polymorphisms noted in men and others in women. There are also differences in terms of endothelial function and hemostasis (women have higher levels of fibrinogen and factor VII). Some of these or other mechanisms may eventually be identified as the reason for gender differences in the development and progression of CAD.

In recent years, microvascular dysfunction has been postulated as the underlying process leading to symptoms of CHD in some women. It is postulated that estrogen withdrawal in perimenopausal and postmenopausal women leads to impaired vasodilatation and/or enhanced vasoconstriction. This hypothesis stems from the diagnosis of **cardiac syndrome X, in which patients, predominantly postmenopausal women, exhibit symptoms of typical angina pectoris with transient abnormal electrocardiogram (ECG) and/or stress perfusion studies**, yet most have minimal angiographic evidence of CAD when undergoing left heart catheterization (LHC). Further studies are needed to better define the populations at risk for microvascular dysfunction and determine potential therapeutic interventions.

Stress (Takotsubo) cardiomyopathy is another novel disease entity affecting predominantly postmenopausal women, accounting for over 80% of cases. Alternatively known as apical ballooning syndrome or broken heart syndrome, stress cardiomyopathy is diagnosed when patients, often in the setting of severe emotional distress or physical trauma, present with chest pain, anterior ST elevations, mildly abnormal cardiac biomarkers, and characteristic appearance of an akinetic, ballooning apex on echocardiography or left ventricular (LV) ventriculogram. Angiography often reveals normal-appearing coronary vessels. The etiology of stress cardiomyopathy and the reason behind such strong female predilection are unclear. Catecholamine surge with stress has been implicated in a number of patient cohorts with this cardiomyopathy. The prognosis of stress cardiomyopathy is quite good, as the majority of patients regain systolic function within 6 months.

III. GENDER DIFFERENCES IN RISK FACTORS

A. Diabetes mellitus. Diabetes affects more women than men after the age of 60. It is associated with a higher incremental risk for CAD (two to four times the risk of women

without diabetes) and drastically increases the mortality of MI in women, much more so than in men. Type 2 diabetes is associated with other components of the metabolic syndrome, all of which increase risk for CAD. Diabetes is also strongly associated with the development of heart failure, with or without preserved ejection fraction.

- B. Hypertension (HTN).** More than 73% of women aged 65 to 74 years have HTN. The risk of developing HTN increases for women if they are 20 pounds or more overweight, have a family history of HTN, or have reached menopause. Risk for CVD related to HTN rises steeply with age, although most studies show that treatment attenuates this risk.
- C. Hyperlipidemia.** Lipid fractions in women are affected by their menopausal status. Premenopausal women have lower low-density-lipoprotein cholesterol (LDL-C) levels and higher high-density-lipoprotein cholesterol (HDL-C) levels than age-matched men. With aging, LDL-C increases and HDL-C decreases, causing the risk of CAD to increase. Total cholesterol and LDL-C are less predictive in women, unlike HDL-C, which is inversely associated with the risk. Non-HDL-C and total cholesterol to HDL-C ratio are more predictive in women than in men. In addition, triglycerides are a more potent independent predictor of CAD, especially in older women.
- D. Cigarette smoking.** This is the single most preventable risk factor. Smoking leads to more CVD deaths than any other risk factor, likely owing to its effects of increasing inflammation, thrombosis, and oxidation of LDL-C. Smoking also has an antiestrogen effect, inducing unfavorable changes in lipid levels. There is a sixfold to ninefold increased risk of MI in female smokers compared with age-matched nonsmokers; in fact, the risk from smoking is equivalent to the risk of weighing about 42 kg more than a nonsmoking woman. However, with smoking cessation, risk is cut in half after 1 year without smoking and eventually declines back to baseline nonsmoker's risk.
- E. Obesity and metabolic syndrome.** More than 30% of American women are obese, and this number continues to climb. In women, obesity and body fat distribution (i.e., abdominal location) are independent risk factors for CAD. As shown by an examination of a cohort of 115,195 women from the Nurses' Health Study, risk of death from CVD increased with increasing body mass index (BMI). Abdominal fat accumulation leads to the development of other components of the metabolic syndrome, such as HTN, diabetes, and hypertriglyceridemia. Obesity is also associated with elevated levels of C-reactive protein (CRP), more so in women.

Women with the metabolic syndrome more often have subclinical CAD than men. A substudy from the National Heart, Lung, and Blood Institute-sponsored WISE (Women's Ischemia Syndrome Evaluation) study revealed that women with the metabolic syndrome have twice the risk for CHD-related events compared with age-matched women without the metabolic syndrome. The metabolic syndrome is defined by the National Cholesterol Education Program Adult Treatment Panel-III in women as the presence of three or more of the following components:

- (1) Waist circumference > 35"
 - (2) Fasting triglycerides > 150 mg/dL
 - (3) HDL-C < 50 mg/dL
 - (4) HTN (systolic blood pressure \geq 130 mm Hg, diastolic blood pressure \geq 85 mm Hg, or use of antihypertensive drug therapy)
 - (5) Fasting glucose \geq 110 mg/dL
- F. Estrogen/menopause.** Postmenopausal women have more CVD risk factors, such as obesity, HTN, and hyperlipidemia, likely owing to the changing hormonal environment (estrogen levels are one-tenth the premenopausal level). The predominant source of estrogen changes from estradiol in the premenopausal state to the much weaker hormone estrone (produced by the conversion of androgens in peripheral adipose tissue) during menopause. Animal studies have shown that estrogen can have favorable CV effects, reducing cellular hypertrophy, enhancing vessel wall elasticity, and providing antioxidative and anti-inflammatory actions.

As part of the WISE study results, endogenous estrogen deficiency in young women was shown to be a strong risk factor for CHD, with a 7.4-fold increased risk. Because of the protection from CAD afforded for premenopausal women, there was early enthusiasm for the use of hormone replacement therapy (HRT) to prevent CVD in postmenopausal women, sparked by data from observational studies. However, multiple randomized, placebo-controlled trials over recent years have shown evidence of increased risk for CVD with HRT, such that it is no longer recommended for primary or secondary prevention of CVD (see Section VI.F).

- G. Physical inactivity.** As women age, they become less physically active than their male counterparts. This contributes to weight gain and predisposes to the development of diabetes and HTN. In addition, with the cessation of estrogen production with menopause, there is increased abdominal fat deposition, further predisposing to CAD. There is a strong inverse association between the activity level and incidence of CV events (see Table 46.2).
- H. Novel risk factors.** It has been increasingly realized that the traditional risk factors underestimate CHD risk in women. For this and other reasons, research has been focused on identifying other novel biomarkers that can better define a person's risk. Multiple biomarkers have been investigated to various degrees (e.g., high-sensitivity C-reactive protein [hsCRP], brain natriuretic peptide, and fibrinogen), but the greatest promise appears to be with hsCRP. As part of the Women's Health Study, over 27,000 healthy American women had their CRP and LDL-C levels measured. The women were then followed for a mean of 8 years for the occurrence of the primary end point (MI, ischemic stroke, coronary revascularization, or death from CVD). Although minimally correlated with each other, both CRP and LDL-C levels had strong linear relationships with CVD events, with CRP being the stronger predictor. Each biomarker tended to identify different high-risk groups, but better prognostic values were obtained when both were used together. These data suggest that CRP shows promise when added to traditional risk factors for prediction of long-term risk.

IV. GENDER DIFFERENCES IN CLINICAL MANIFESTATIONS. Women often present differently than men, potentially because of differences in underlying pathophysiology. This is particularly true for diabetic women. Women usually present at an older age, usually 5 to 10 years later than men, and have more comorbidities on presentation than men do. As such, once the diagnosis of CAD is made, women are at higher risk for adverse outcomes.

- A.** Like men, women can present with typical symptoms of angina, such as substernal **chest pain** and **dyspnea on exertion** that is relieved by rest. These symptoms more often occur in older women, who present more similarly to men.
- B.** Women can also present with **atypical chest pain; shortness of breath; neck, shoulder, or arm pain; diaphoresis; and nausea/vomiting.**
- C.** Women are more likely to have subtle symptoms that require detailed history-taking to elicit, such as **chest "pressure or tightness," lightheadedness, palpitations, or fatigue.** Women most often have symptoms that occur at rest, wake them from sleep, or occur in times of psychological stress.
- D.** Women more often present acutely without preexisting prodromes of symptoms or with **sudden cardiac death.**

V. GENDER DIFFERENCES IN ASSESSMENT

- A. Exercise electrocardiography.** Exercise electrocardiography, the most frequently employed diagnostic modality, is useful only in women with normal baseline ECGs and with the ability to undergo moderate or high levels of exercise (generally on the treadmill). An abnormality is identified if there is ≥ 1 mm of ST-segment depression or elevation. Generally, exercise ECG has lower sensitivity and specificity than other modalities, and this is even more prominent in women (sensitivity and specificity

60% to 70% in women vs. 80% in men). This difference is not well understood, but it has been attributed to several factors, such as lower overall prevalence of CAD in women or more submaximal stress tests, owing to the inability of women to exercise to sufficient levels to produce a diagnostic test. If women are unable to achieve at least five metabolic equivalents (METs), studies have shown that they are at increased risk for future CV events.

- B. Stress echocardiography (transthoracic echocardiography [TTE]).** Stress TTE tends to have higher specificity and lower sensitivity than stress perfusion imaging, as wall motion abnormalities occur later than perfusion abnormalities. However, stress TTE has the advantages of eliminating radiation exposure, decreasing cost, and providing the ability to assess LV function and cardiac structures. It has been shown to be a cost-effective initial strategy for determining CV risk in patients at intermediate risk as compared with stress electrocardiography, and we now use it as a first-line diagnostic test for CAD in women.
- C. Stress myocardial perfusion scan.** Because of the limited sensitivity and specificity of exercise ECG in women, other modalities are frequently employed to assess the risk of CAD. The most frequently used test is the single-photon emission computed tomography (SPECT) scan, a radionuclide-based technique. Because alterations in myocardial perfusion generally occur earlier than electrocardiographic changes or wall motion abnormalities, this test is more sensitive than exercise ECG or echocardiography for estimating risk in either gender. For those individuals unable to exercise or attain target heart rates, adenosine or dipyridamole can be used as a pharmacologic stress agent. To increase specificity, the higher energy isotopes (technetium 99m) are recommended in women to reduce the soft tissue attenuation artifacts (influenced by both breast tissue and obesity) that tend to occur anteriorly and laterally. Other limitations of SPECT can be critical in women. Because women have smaller hearts, the limitations in spatial resolution of SPECT can lead to small areas of hypoperfusion being missed.
- D. Magnetic resonance imaging (MRI).** Although not as commonly used, this is an emerging modality owing to its ability to evaluate for subendocardial ischemia, precisely assess LV function and mass, and evaluate the anatomy of the myocardium and vasculature. MRI provides the best spatial and temporal resolution, which is thought to be especially helpful when imaging women. Other benefits include the ability to detect ischemia by identifying altered metabolism. This is achieved by magnetic resonance spectroscopy, which can detect alterations in high-energy phosphates and identify these areas of altered metabolism. Areas of altered metabolism have been shown in reports from the WISE study to be indicative of microvascular dysfunction, as women with nonobstructive CAD assessed by LHC have altered high-energy phosphate ratios indicative of ischemia identified by spectroscopy.
- E. Coronary angiography.** Diagnostic coronary angiography is the gold standard for diagnosing CAD in both men and women. When evaluated by LHC, however, women more often have minimal to no obstructive CAD. For reasons not fully elucidated, women tend to experience vascular complications such as bleeding and renal failure related to diagnostic LHC more frequently than men do. The occurrence of a complication is thought to be related to older age at the time of presentation, smaller body size, smaller vessel size, and higher prevalence of diabetes. A transradial approach to diagnostic and interventional coronary procedures has been shown to be safe and lead to less bleeding complications than transfemoral catheterizations in both men and women and thus might be considered the primary catheterization approach in women.

VI. GENDER DIFFERENCES IN THERAPIES. Most CVD in women, as in men, can be prevented if risk factor modification occurs early and aggressively. Until recently, most of the clinical trial data, on which the guidelines for prevention and treatment of both genders are based, were derived from trials conducted largely in men. This information

had been extrapolated to women because gender-specific trial data were lacking. Because of this uncertainty, more recent clinical trials have offered insights into gender-specific results, allowing for evidence-based guidelines for disease prevention and treatment in women. However, with only a few exceptions, the guidelines are the same for both men and women. The gender-specific results are highlighted here; for a full discussion, please see appropriate sections of previous chapters.

A. Aspirin. Aspirin (ASA) is the principal antiplatelet agent in patients with CAD. Its benefit in secondary prevention, as well as in acute coronary syndrome (ACS), STEMI, and after revascularization (coronary artery bypass grafting or percutaneous coronary intervention [PCI]), is well known and discussed elsewhere. However, there are very few gender-specific data in these instances, so most recommendations are extrapolated from trials conducted largely in men.

The role of ASA in primary prevention of CAD in women is better defined. Early data suggested that ASA may be protective as primary prevention for future CVD events in women, as it is in men. However, as part of the Women's Health Study, 39,876 healthy women older than age 45 were randomized to either ASA 100 mg on alternate days or placebo, and they were followed for the incidence of CV events (nonfatal MI, nonfatal stroke, or CV death) over 10 years. **Despite a 24% reduction in ischemic stroke, ASA had no benefit over placebo in reducing MI or CV death.** However, ASA did appear protective as primary prevention in those women aged 65 years or older, as it significantly decreased the risk of both MI and stroke in this age group. There was also an increased risk of bleeding observed, which highlights the need for an individualized approach to the use of ASA as primary prevention in older women. **Using "low-dose aspirin", i.e., 81 or 75 mg daily rather than the "full dose" of 325 mg daily, in women might confer effective CV protection without excessive bleeding risk.**

B. Thienopyridines. For two decades, the most commonly used agents in this class are clopidogrel and ticlopidine. The use of ticlopidine has decreased significantly with evidence of adverse effects, including neutropenia and thrombotic thrombocytopenic purpura. These agents have proven beneficial, when given with ASA, to reduce the rate of stent thrombosis after PCI. Clopidogrel has also shown benefit in secondary prevention of CAD, ACS, and STEMI (discussed in detail elsewhere). Few of the clinical trials using clopidogrel have given gender-specific data, but there are some data available for specific settings.

In the substudy of the Clopidogrel in Unstable angina to prevent Recurrent Events (CURE) trial, in which the patients received PCI (PCI-CURE), 2,658 patients with non-ST-segment elevation ACS undergoing PCI were randomly assigned to aspirin plus clopidogrel or placebo for 9 months. Of the study population, 30.2% were women. Clopidogrel plus aspirin long-term therapy improved outcomes in those patients who received PCI. This was more significant in men, but a definite trend toward benefit in women was evident as well. Similar results were seen for women in the Clopidogrel for the Reduction of Events During Observation (CREDO) trial, where 29% of the 2,116 patients were women. The CREDO trial showed benefit of post-PCI therapy with ASA and clopidogrel out to 1 year of therapy, again with a trend toward benefit in women. CREDO trial also revealed, by subgroup analysis, equally beneficial effects of a loading dose of clopidogrel in men and women.

Prasugrel is the most recent addition to the class of oral antiplatelet agents. Pharmacokinetic studies have shown that prasugrel achieves faster onset and greater extent of platelet inhibition compared with clopidogrel. It was FDA approved for patients with ACS undergoing PCI in 2009. In the Trial to Assess Improvements in Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel—Thrombolysis in Myocardial Infarction 38 (TRITON-TIMI 38), prasugrel had lower primary end points (CV death, nonfatal MI, or nonfatal stroke) than clopidogrel in 13,608 patients (one-fourth of whom were women) with moderate- to high-risk ACS with

scheduled PCI (9.9% vs. 12.1%). However, the prasugrel group did have higher rates of bleeding particularly in patients with history of stroke or transient ischemic attack, patients aged 75 years or older, or patients weighing less than 60 kg. These data are especially important for women, as there was slightly less observed benefit with prasugrel therapy in women—this difference is likely related to increased risk of bleeding of antiplatelet use of any kind in woman, as shown by a recent post hoc analysis of the TRITON-TIMI 38 data.

- C. **Statins.** Prior to the last several years, almost 20,000 women participated in clinical trials of statin use, only about one-fourth of overall participants. Two exceptions to this were the Prospective Study of Pravastatin in the Elderly at Risk (PROSPER) trial (50% women) and the lipid-lowering therapy arm of the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT-LLT), which had 49% female participation. ALLHAT-LLT, a primary prevention trial, did not release gender-specific results; PROSPER, having patients with history of or at risk for CVD, did not show a statistically significant benefit in women.

Otherwise, the other major primary and secondary prevention trials of statin therapy have shown similar benefit with statin therapy on reduction of CV events in men and women. The largest number of women enrolled to date in a statin trial was the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) trial. With over 17,000 patients enrolled (38% of them women), this trial demonstrated encouraging evidence for the benefit of statin therapy in decreasing vascular events in both women and men with “normal” serum LDL-C and elevated serum CRP levels, with a ~45% reduction in combined end point of MI, stroke, or death from CV causes. In the Treating to New Targets (TNT) trial, patients who were given intensive lipid control treatment with higher dose of atorvastatin (80 mg) were shown to have a significantly reduced primary end point of a first major CV event (death from CHD, nonfatal MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke) over those on lower dose therapy (atorvastatin 10 mg). Even more encouraging was that this benefit also extended to women. In women (19% of total population) from the TNT trial, the relative and absolute reductions in the primary end point were 27% and 2.7%, respectively; this was actually better than those observed in men, who had 21% and 2.2% reduction, respectively.

- D. **β -Blockers.** There are no gender-specific data for the use of β -blockers in women for primary and secondary prevention, as previous studies have included insignificant numbers of women. However, a meta-analysis of 5,474 patients (1,121 women) enrolled in five randomized trials revealed similar reductions in CV death in men and women with metoprolol.
- E. **Angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs).** With respect to the use of ACE inhibitors in women with LV dysfunction, the data are lacking, because trials have included very few women. Several trials have examined ACE inhibitors in primary and secondary prevention of CV events in patients without LV dysfunction, with conflicting results irrespective of gender. The Heart Outcomes Prevention Evaluation (HOPE) study showed that ACE inhibitors were associated with a mortality reduction in high-risk women that was similar to that in men. The EUROpean trial On reduction of cardiac events with Perindopril in stable coronary Artery disease (EUROPA) could not confirm these beneficial findings in women, as the trial included only 14.5% women, but it did show benefit in men. To date, it appears that data for ACE inhibitors in women are not as favorable as for men; however, this needs to be further delineated.

In terms of ARBs for therapy after MI, only two trials have been reported—VALsartan in Acute myocardial iNfarcTion (VALIANT) and OPTimal Trial In Myocardial Infarction with Angiotensin II Antagonist Losartan (OPTIMAAL). Neither of these reported gender-specific data.

- F. Hormone replacement therapy.** Despite beneficial evidence from previous observational studies, recent data from randomized controlled trials have shown no benefit of HRT in postmenopausal women for preventing CV events. The first of these randomized trials was the Heart and Estrogen/progestin Replacement Study (HERS). In this study of secondary prevention, 2,763 postmenopausal women with CAD were randomized to either 0.625 mg of conjugated equine estrogen plus 2.5 mg of medroxyprogesterone acetate or placebo daily. After an average 4-year follow-up, there was no significant difference in the primary outcome of nonfatal MI or CHD death between the groups. Of interest, however, was the fact that the greatest numbers of CV events were noted within the first year in the HRT group. Not surprisingly, the HRT group had a greater incidence of venous thromboembolism and gallbladder disease.

Because of the high number of CV events in the first year, the investigators thought that beneficial effects of HRT might be observed after time, as it appeared that HRT became more protective by 4 to 5 years of follow-up in the HERS population. With this in mind, the HERS II study followed 2,321 of the original HERS patients, the majority of whom stayed on their original treatment in an open-label format, for an average of 6.8 years. After the longer follow-up, there was still no difference in nonfatal MI or CHD death between the groups.

To delineate the role of HRT in primary prevention of CV events, the Women's Health Initiative randomized 16,608 healthy, postmenopausal women to the same estrogen–progestin combination used in HERS or placebo. The primary end points were the same, nonfatal MI or death due to CHD. After a mean 5.2-year follow-up, the trial was stopped by the data and safety monitoring board due to untoward risks in the treatment arm. Estrogen and progestin therapy was associated with an increased risk for CV events, most impressively at 1 year. Despite some favorable effects on lipids, **HRT should not be recommended for either the primary or the secondary prevention of CVD in postmenopausal women.**

- G. Lifestyle modification.** The good news for women is that initiating lifestyle modifications can reduce CV risk by reducing the risk of developing diabetes. As part of the Diabetes Prevention Program Research Group, 3,234 patients (68% women) with impaired glucose tolerance were randomized to placebo, metformin (850 mg twice daily), or lifestyle modification (goal 7% weight loss and at least 150 minutes of physical activity per week). After almost 3 years of follow-up, the lifestyle modification group had a 58% reduction in the incidence of diabetes compared with 31% in the group with metformin. This translates to a decreased risk of CVD.

- H. Folic acid and antioxidants.** Despite previous recommendations to lower homocysteine levels with folic acid and vitamin B supplementation, there is now evidence to discourage this practice. Three randomized trials—the Norwegian Vitamin (NORVIT) study, the HOPE-2 trial, and Women's Antioxidant and Folic Acid Cardiovascular Study (WAFACS)—showed no benefit in reducing CV events. The NORVIT study included both men and women post-MI and randomized the groups to one of four treatments: folic acid, vitamin B₁₂, and vitamin B₆; folic acid and vitamin B₁₂; vitamin B₆ alone; or placebo. Despite lowering of homocysteine levels, the treatment groups had no advantage in terms of reductions in the primary end point of recurrent MI, stroke, or sudden death attributed to CAD. In fact, the group that received all three therapies had a trend toward increased risk. Similar results were seen in the HOPE-2 trial. Therefore, these therapies should not be recommended. In addition, data from the Women's Health Study do not support the use of vitamin E in the primary prevention of CV events.

VII. EVIDENCE-BASED GUIDELINES FOR HEART DISEASE PREVENTION IN WOMEN.

The American College of Cardiology/American Heart Association (ACC/AHA) guidelines emphasize the importance of recognizing the wide-ranging spectrum of CV disease in women. In general, a woman aged 20 years or older is first classified as at high risk, at

risk, or at optimal risk based on the criteria in Table 46.1. Several factors should be evaluated, such as medical history, lifestyle, family history of premature CAD, Framingham risk score, and other genetic conditions, before decision regarding the aggressiveness of preventive therapy is finalized.

TABLE 46.1 Risk Classification of Cardiovascular Disease in Women

High risk	At risk	Optimal risk
<ul style="list-style-type: none"> Known CAD Cerebrovascular disease Peripheral arterial disease End-stage renal or chronic kidney disease Diabetes 10-y Framingham global risk > 10% 	<ul style="list-style-type: none"> Subclinical atherosclerosis (e.g., coronary calcification, carotid plaque, or thickened intima-media) Cigarette smoking Poor diet Physical inactivity Obesity (especially abdominal location) Dyslipidemia (total cholesterol > 200 mg/dL, HDL-C < 50 mg/dL, or treated for dyslipidemia) HTN (SBP > 120 mm Hg, DBP > 80 mm Hg, treated HTN, or history of pregnancy-induced HTN) Family history of premature CAD (< 55 y in men, < 65 y in women) Metabolic syndrome or history of preeclampsia or gestational diabetes Poor exercise capacity on exercise treadmill test and/or abnormal heart rate recovery after stopping exercise Family history of premature CVD occurring in first-degree relatives in men < 55 y of age or in women < 65 y of age Autoimmune diseases (e.g., SLE or RA) 	<ul style="list-style-type: none"> Fasting blood glucose < 100 mg/dL (untreated) Nonsmoker Healthy (Dietary Approaches to Stop Hypertension (DASH)-like) diet Physical activity goal for adults < 20 y of age: > 150 min/wk moderate intensity, > 75 min/wk vigorous intensity, or combination BMI < 25 kg/m² Total cholesterol < 200 mg/dL (untreated) BP < 120/< 80 mm Hg (untreated)

CAD, coronary artery disease; BMI, body mass index; HDL-C, high-density-lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure; BP, blood pressure; CVD, cardiovascular disease; HTN, hypertension. SLE, systemic lupus erythematosus; RA, rheumatoid arthritis.

Adapted from ACC/AHA guidelines 2011 update. *JACC*. 2011;57:1404–1423.

The guidelines are grouped into three main areas: lifestyle interventions, major risk factor interventions, and preventive drug interventions. Table 46.2 lists the class I and class IIa recommendations for primary or secondary prevention of CVD in women. These guidelines are suggested as a starting point, with therapy tailored to the needs of each individual patient.

TABLE 46.2 Evidence-Based Guidelines for Prevention of Heart Disease in Women

Lifestyle interventions	Major risk factor interventions	Preventive drug interventions
• Class I recommendations		
Smoking cessation	Maintain optimal BP (< 120/80 mm Hg) with lifestyle modification	ASA in high-risk women (known CAD, cerebrovascular disease, PAD, AAA, ESRD, CKD, diabetes, and 10-y Framingham risk > 20%)
Exercise: 150 min/wk of moderate intensity exercise (e.g., brisk walking), 75 min/wk of vigorous intensity exercise (e.g., running), or combination	Pharmacotherapy for BP \geq 140/90 mm Hg (\geq 130/80 mm Hg in CKD or diabetes). Thiazide should be initial agent unless compelling indications for β -blockers and/or ACE inhibitor/ARB exist (e.g., ACS/MI)	Clopidogrel therapy for high-risk women intolerant of ASA
Weight loss to BMI < 25 kg/m ² and waist circumference \leq 35"	Control of lipids through lifestyle modification (LDL-C < 100 mg/dL, HDL-C > 50 mg/dL, triglycerides < 150 mg/dL, and non-HDL-C [total cholesterol-HDL-C] < 130 mg/dL)	β -Blockers for at least 1 y and up to 3 y in women after MI and ACS, with normal LV function. Use indefinitely if LV dysfunction present
Cardiovascular rehabilitation in those with recent ACS or PCI, angina, and recent CVA, PAD, or CHF	Pharmacotherapy of lipids in those with CAD or diabetes to goal LDL-C < 100 mg/dL	ACE inhibitors in those after MI or with clinical CHF, LV dysfunction (LVEF \leq 40%), or diabetes. If intolerant of ACE inhibitor, ARB can be substituted
Diet counseling to promote intake of fruits and vegetables, whole grain and high-fiber foods, and fish at least two times per week. Limit consumption of saturated fat, cholesterol, alcohol, sodium, and <i>trans</i> -fatty acids	Pharmacotherapy of lipids in those with LDL-C \geq 130 mg/dL after lifestyle modification and presence of multiple risk factors (or if LDL-C \geq 160 mg/dL in those with multiple risk factors, even if Framingham risk < 10%) Pharmacotherapy of lipids in those with LDL-C \geq 190 mg/dL regardless of other risk factors	Aldosterone blockade after MI in symptomatic women with LVEF \leq 40% who are without renal dysfunction or hyperkalemia and who are already on an ACE inhibitor and β -blocker

TABLE 46.2 Evidence-Based Guidelines for Prevention of Heart Disease in Women (Continued)

Lifestyle interventions	Major risk factor interventions	Preventive drug interventions
	Maintain HbA _{1c} < 7% in diabetics	
• Class IIA recommendations		
	Goal LDL-C < 70 mg/dL is reasonable in the very high risk (known CAD + multiple major risk factors, severe and poorly controlled risk factors, or diabetes)	Low-dose ASA therapy (81 mg daily or 100 mg on alternate days) in women ≥65 y if benefits outweigh risk of bleeding
• Class IIB recommendations		
ω-3 Fatty acid in the form of fish or capsule (e.g., EPA 1,800 mg/d) may be considered in women with hypercholesterolemia or hypertriglyceridemia for primary or secondary prevention	Pharmacotherapy with niacin or fibrates when HDL-C is low or non-HDL-C is elevated in high-risk women (after LDL-C goal reached)	

AAA, abdominal aortic aneurysm; ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; ASA, aspirin; BMI, body mass index; BP, blood pressure; CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; EPA, eicosapentaenoic acid; ESRD, end-stage renal disease; HbA_{1c}, glycosylated hemoglobin; HDL-C, high-density-lipoprotein cholesterol; LDL-C, low-density-lipoprotein cholesterol; LV, left ventricular; LVEF, left ventricular ejection fraction; MI, myocardial infarction; mm Hg, millimeters of mercury; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention.

Adapted from ACC/AHA guidelines 2011 update. *JACC*. 2011;57:1404–1423.

In general, it is suggested that the initial evaluation begin with a complete history, specifically eliciting symptoms of CVD, as well as a complete physical examination, with particular attention to blood pressure, BMI, and waist size. Laboratory evaluation should follow, including fasting lipids and glucose levels. During the evaluation, assessment of Framingham risk should be performed, as well as depression screening in those women with known CVD.

All class I lifestyle interventions should be employed in **all women**, regardless of risk level.

If the woman is at **high risk** (established CAD, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm, diabetes, chronic kidney disease, or Framingham risk > 20%), the **class I major risk factor and preventive drug interventions** should be initiated (see Table 46.2). Consideration should also be given to some of the class II recommendations, particularly the **LDL-C goal of < 70 mg/dL**.

There are some interventions that should not be considered under any circumstances. Table 46.3 lists those therapies that are **contraindicated** based on the results of recent clinical trials.

Novel risk factors, such as CRP (used as inclusion criteria in JUPITER), and newer screening modalities may have a role in the future, but this role is not yet defined. Further research is needed in these areas before they can be incorporated into the guidelines.

TABLE 46.3 Class III Interventions (Ineffective, Possibly Harmful in Cardiovascular Disease Prevention in Women)

Hormone replacement therapy or selective estrogen receptor modulators
Antioxidant vitamin supplementation (vitamin E, vitamin C, and β -carotene)
Folic acid with or without vitamin B ₆ or B ₁₂ (Folic acid supplementation should be used in the childbearing years to prevent neural tube defects)
ASA in healthy women < 65 y

ASA, aspirin.

Adapted from ACC/AHA guidelines 2011 update. *JACC*. 2011;57:1404–1423.

VIII. CURRENT PROGRESS AND FUTURE INNOVATIONS. Despite clinical trial data that document the benefits of multiple therapeutic interventions, women are still inadequately treated. In fact, despite the vast amount of data on statins, the 1999 to 2000 National Health and Nutrition Examination Survey (NHANES) reported that only 10.2% of women with hyperlipidemia were receiving therapy compared with 14% of men. Men, when treated, were also much more likely to reach their goal LDL-C. Strikingly, in a study of patients receiving care in an academic medical practice, women with diabetes were the group most likely to be inadequately treated for their modifiable CVD risk factors. Furthermore, even higher risk patients (women with ACS) have been shown to be less aggressively treated than their male counterparts.

Despite the aggressive campaigns by the AHA and other organizations, women are still not well informed regarding their personal risk for heart disease. In the 2003 AHA-sponsored survey of women, only 40% considered themselves either “very well” or “well” informed about heart disease, even fewer in the most at-risk minorities. Although nearly all of the women were comfortable discussing their risk for CHD with their physician, only 38% reported that their physician had actually discussed this risk with them. This highlights the need for health-care providers to bridge this knowledge gap and seize the opportunities to discuss risks and risk factor modification with patients. Subsequently, health-care providers should aggressively treat the appropriate women based on guideline recommendations in order to improve long-term outcomes.

The population is aging, and the incidence of CVD is only likely to increase, unless we begin to institute preventive therapies earlier, and to aggressively continue them over a woman's lifespan. More attention should be paid by health-care providers to promote a woman's awareness of her risk for CVD as well as instituting therapies aggressively aimed at prevention that are tailored to a woman's specific needs.

Further research is needed in the area of gender-specific differences in CAD and all of its manifestations, as well as many of the pharmacologic and interventional therapies used in its treatment. Research that delves further into novel risk factors and the additional value that can be provided over traditional risk factors in terms of assessing risk for CVD, especially in women, is needed as well. Ongoing genetics research, as well as research related to sex hormones, could also provide useful information for tailoring gender-specific therapy. Novel imaging strategies such as cardiac Positron Emission Tomography (PET) with assessment of myocardial blood flow (MBF), are being studied and may provide important information. This may be especially important in women, given the difficulty with noninvasive diagnosis of obstructive CAD. Hopefully, once some of these diagnostic and therapeutic modalities become available, there will be appreciable changes in the occurrence and outcomes of CVD in women.

ACKNOWLEDGMENTS: *The author wishes to thank Dr. Kellan Ashley for contributions to this chapter in an earlier edition.*

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SECTION

IX

Noninvasive Assessment

EDITOR

Brian P. Griffin

Exercise Electrocardiographic Testing

I. INTRODUCTION

A. Exercise electrocardiographic testing is a field in flux. In the past decade, it has become clear that ST-segment changes during exercise have low sensitivity and specificity in the evaluation of coronary artery disease (CAD) and are poor predictors of risk. This may be partially due to the fact that stable obstructive plaques, which typically result in exercise-mediated ischemia, are less relevant to myocardial infarction (MI) and sudden cardiac death than unstable nonobstructive plaques. Although the bulk of obstructive CAD screening has now shifted towards various stress imaging modalities, many of the physiologic parameters measured during exercise have emerged as powerful prognostic indicators. As such, the main uses of exercise electrocardiographic testing should be *evaluation of prognosis* and as a *gateway to other imaging modalities*. Stand-alone testing for CAD diagnosis is reserved for patients with *intermediate risk for CAD* and should be ordered with a careful understanding of the limitations of the test for this purpose.

1. The **advantages** of exercise electrocardiographic testing are its ability to assess a variety of prognostic markers, most importantly **functional capacity**, which is a powerful predictor of mortality, widespread availability, safety, ease of administration, and relatively low cost. The assessment of functional capacity may be particularly advantageous in patients with valvular heart disease and congenital heart disease whereupon recognition of functional limitation is often difficult to ascertain by history alone.
2. **Disadvantages.** As a screening test for CAD in persons without symptoms, exercise electrocardiography is generally not helpful or indicated. It has a **low sensitivity and specificity**, which can be improved with careful selection of the patient population undergoing testing.
- B. **Submaximal exercise electrocardiographic testing** (i.e., testing at submaximal heart rate, discussed later) is a useful assessment before hospital discharge for **patients who have had MI**. The advantages are as follows:
 1. It assists in setting **safe levels** of exercise (exercise prescription) and reassuring patients and families.
 2. It is beneficial in **optimization of medical therapy**, in triage for intensity of follow-up testing and care, and in recognition of exercise-induced ischemia and arrhythmias.
 3. For patients with uncomplicated MI who have received reperfusion therapy, submaximal exercise testing may be safely **performed as early as 3 days after MI**, with maximal exercise testing 3 to 6 weeks later.

II. **INDICATIONS.** The indications for exercise electrocardiographic testing are divided on the basis of the degree of likelihood of disease or severity of diagnosed disease, use in valvular heart disease, and use in congenital heart disease (Table 47.1).

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing**Exercise testing in the diagnosis of obstructive CAD****Class I^a**

Adult patients (including those with complete right bundle branch block or < 1 mm of resting ST depression) with an intermediate pretest probability of CAD on the basis of sex, age, and symptoms

Class IIa

Patients with vasospastic angina

Class IIb

Patients with a high pretest probability of CAD on the basis of age, symptoms, and sex

Patients with a low pretest probability of CAD on the basis of age, symptoms, and sex

Patients with < 1 mm of baseline ST depression and taking digoxin

Patients with electrocardiographic criteria of left ventricular hypertrophy and < 1 mm of baseline ST depression

Class III

Patients with baseline electrocardiographic abnormalities

Preexcitation (Wolff-Parkinson-White) syndrome

Electronically paced ventricular rhythm

> 1 mm of resting ST depression

Complete left bundle branch block

Patients with a documented myocardial infarction or prior coronary angiographic findings of disease and an established diagnosis of CAD (ischemia and risk can be determined with testing)

Risk assessment and prognosis among patients with symptoms or a history of CAD**Class I**

Patients undergoing initial evaluation with suspected or known CAD (exceptions in class 2b), including those with complete right bundle branch block or < 1 mm of resting ST depression

Patients with suspected or known CAD previously evaluated, now presenting with marked change in clinical status

Low-risk unstable angina patients 8–12 h after presentation who have been free of active ischemic or heart failure symptoms

Intermediate-risk unstable angina patients 2–3 d after presentation who have been free of active ischemic or heart failure symptoms

Class IIa

Intermediate-risk unstable angina patients with initial cardiac markers that are normal, a repeat electrocardiographic study without significant change, cardiac markers 6–12 h after symptom onset that are normal, and no other evidence of ischemia during observation

Class IIb

Patients with baseline electrocardiographic abnormalities

Preexcitation (Wolff-Parkinson-White) syndrome

Electronically paced ventricular rhythm

1 mm or more of resting ST depression

(Continued)

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing (Continued)

Complete left bundle branch block or any interventricular conduction defect with QRS duration > 120 milliseconds

Patients with a stable clinical course who undergo periodic monitoring to guide treatment

Class III

Patients with severe comorbidity likely to limit life expectancy and/or candidacy for revascularization

High-risk unstable angina patients

After acute myocardial infarction

Class I

Before discharge for prognostic assessment, activity prescription, or evaluation of medical therapy (submaximal at about 4–6 d)

Early after discharge for prognostic assessment and cardiac rehabilitation if the predischARGE exercise test was not performed (symptom limited, about 14–21 d)

Late after discharge for prognostic assessment, activity prescription, evaluation of medical therapy, and cardiac rehabilitation if the early exercise test was submaximal (symptom limited, about 3–6 wk)

Class IIa

After discharge for activity counseling or exercise training as part of cardiac rehabilitation of patients who have undergone coronary revascularization

Class IIb

Patients with electrocardiographic abnormalities

Complete left bundle branch block

Preexcitation (Wolff-Parkinson-White) syndrome

Left ventricular hypertrophy

Digoxin therapy

Electronically paced ventricular rhythm

> 1 mm of resting ST depression

Periodic monitoring for patients who continue to participate in exercise training or cardiac rehabilitation

Class III

Severe comorbidity likely to limit life expectancy or candidacy for revascularization

Patients with acute myocardial infarction and uncompensated congestive heart failure, cardiac arrhythmia, or noncardiac conditions that severely limit exercise ability

Before discharge, patients who have been selected for or have undergone cardiac catheterization (stress imaging tests are recommended)

Exercise testing for persons without symptoms or known CAD

Class I

None

Class IIa

Asymptomatic persons with diabetes mellitus to start vigorous exercise

Class IIb

Persons with multiple risk factors

TABLE 47.1 *Continued*

Men older than 45 y and women older than 55 y without symptoms
 Who plan to start vigorous exercise (especially if sedentary)
 Who are involved in occupations in which impairment might affect public safety
 Who are at high risk for CAD because of other diseases

Class III

Routine screening of men or women without symptoms

Exercise testing for persons with valvular heart disease**Class I**

None

Class IIa

Patients with chronic AR and equivocal symptoms to assess functional capacity and symptomatic response

Class IIb

Asymptomatic patients with AS may be considered to elicit exercise-induced symptoms and abnormal blood pressure responses

In asymptomatic or symptomatic patients with chronic AR (with radionuclide angiography) for assessment of left ventricular function

Class III

Exercise testing should not be performed in symptomatic patients with AS

Exercise testing for persons with congenital heart disease**Class I**

None

Class IIa

Asymptomatic young adults < 30 y of age to determine exercise capability, symptoms, and blood pressure response

Adolescent or young adult patient with AS who has a Doppler mean gradient > 30 mm Hg or a peak velocity > 50 mm Hg if the patient is interested in athletic participation or if the clinical findings and Doppler findings are disparate

Asymptomatic young adult with a mean Doppler gradient > 40 mm Hg or a peak Doppler gradient > 64 mm Hg or when the patient anticipates athletic participation or pregnancy

As part of the initial evaluation of adolescent and young adult patients with TR and serially every 1–3 y

In patients with atrial septal defect with symptoms that are discrepant with clinical findings or to document changes in oxygen saturation in patients with mild or moderate PAH

In patients with subvalvular AS testing to determine exercise capability, symptoms, ECG changes or arrhythmias, or increase in LVOT gradient is reasonable in the presence of otherwise equivocal indications for intervention

In patients with supravulvular AS (along with other imaging modalities) testing can be useful to evaluate the adequacy of myocardial perfusion

Class IIb

In patients with aortic coarctation, testing may be performed at intervals determined in consultation with the regional ACHD center

(Continued)

TABLE 47.1 ACC/AHA Guidelines for Exercise Testing (Continued)**Class III**

Patients with atrial septal defect or patent ductus arteriosus with severe PAH
 Symptomatic patients with AS or those with repolarization abnormality on ECG or systolic dysfunction on echocardiography

^a*Class 1*, conditions for which there is evidence or agreement that a given procedure or treatment is useful and effective; *Class 2*, conditions for which there is conflicting evidence or a divergence of opinion about the usefulness or efficacy of a procedure or treatment; *Class 2a*, weight of evidence or opinion is in favor of usefulness and efficacy; *Class 2b*, usefulness or efficacy is less well established on the basis of evidence and opinion; *Class 3*, conditions for which there is evidence or general agreement that the procedure or treatment is not useful or effective and in some cases may be harmful. CAD, coronary artery disease; AR, aortic regurgitation; AS, aortic stenosis; TR, tricuspid regurgitation; PAH, pulmonary arterial hypertension; ECG, electrocardiogram; LVOT, left ventricular outflow tract; ACHD, adult congenital heart disease.

From Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 2002;40:1531–1540, with permission. Adapted from Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. 2008;52:e1–e142 and from Warnes CA, Williams RG, Bashore TM, et al. ACC/AHA 2008 guidelines for the management of adults with congenital heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (writing committee to develop guidelines for the management of adults with congenital heart disease). *J Am Coll Cardiol*. 2008;52:1890–1947.

III. CONTRAINDICATIONS. Contraindications to exercise testing are divided into absolute and relative categories (Table 47.2).

IV. LIMITATIONS OF EXERCISE ELECTROCARDIOGRAPHIC TESTING. Before ordering an exercise electrocardiography test, the physician should have an understanding of Bayes' theorem and the limitations of the test.

- A. Bayes' theorem** states that the probability of a positive test result is affected by the likelihood (i.e., conditional probability) of a positive test result among the population that has undergone the test (i.e., pretest probability). The higher the probability that a disease is present in a given individual before a test is ordered, the higher is the probability that a positive test result is a true-positive test result. Pretest probability is determined on the basis of symptoms, age, sex, and risk factors and can be divided into very low, low, intermediate, and high (Table 47.3).
- B. Sensitivity and specificity.** The likelihood that an abnormal electrocardiographic finding indicates CAD is much higher for an older person with multiple risk factors than for a young person with no risk factors. Sensitivity and specificity vary with the population being tested.
 1. Exercise electrocardiographic testing is **best used** in the evaluation of a patient at intermediate risk with an atypical history or a patient at low risk with a typical history.
 2. For the general population, the sensitivity is 68% and the specificity is 70%. Values are lower for persons at low risk.
 3. Exercise electrocardiographic testing has a higher sensitivity and specificity for **persons at high risk**. For most of these patients, however, invasive testing is preferred for a more definitive diagnosis and possible intervention. Excluding patients with left ventricular hypertrophy or resting ST depression and those taking digoxin also improves sensitivity and specificity.

TABLE 47.2 Contraindications to Exercise Testing**Absolute contraindications**

Acute myocardial infarction (within 2 d)
 High-risk unstable angina
 Uncontrolled cardiac arrhythmias causing symptoms or hemodynamic compromise
 Symptomatic, severe aortic stenosis
 Uncontrolled symptomatic heart failure
 Acute pulmonary embolus or pulmonary infarction
 Suspected or known dissecting aneurysm
 Active or suspected myocarditis, pericarditis, or endocarditis
 Acute noncardiac disorder that may affect exercise performance or be aggravated by exercise (e.g., infection, renal failure, or thyrotoxicosis)
 Considerable emotional distress (psychosis)

Relative contraindications

Left main coronary stenosis or its equivalent
 Moderate stenotic valvular heart disease
 Resting diastolic blood pressure > 110 mm Hg or resting systolic blood pressure > 200 mm Hg
 Electrolyte abnormalities (e.g., hypokalemia and hypomagnesemia)
 Fixed-rate pacemaker
 High-degree atrioventricular block
 Frequent or complex ventricular ectopy
 Ventricular aneurysm
 Uncontrolled metabolic disease (e.g., diabetes, thyrotoxicosis, and myxedema)
 Chronic infectious disease (e.g., mononucleosis, hepatitis, and acquired immunodeficiency syndrome)
 Neuromuscular, musculoskeletal, or rheumatoid disorders exacerbated by exercise
 Advanced or complicated pregnancy
 Hypertrophic cardiomyopathy and other forms of outflow tract obstruction
 Mental impairment leading to inability to cooperate

Adapted from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's Guidelines for Exercise Testing and Prescription*. Baltimore, MD: Williams & Wilkins, 1995; from Fletcher GF, Fletcher GF, Blair SN, et al. Statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 1992;86:340–344; and from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol*. 2002;40:1531–1540.

- C. Positive predictive value (PPV).** After pretest probability and the sensitivity and specificity are known, PPV can be calculated. PPV is a measure of the likelihood that an abnormal test finding represents a true-positive result. It is highly dependent on pretest probability (i.e., prevalence of disease) in the population being tested. For example, in a population at low risk, the PPV of electrocardiographic exercise testing is only 21%, but in a population at high risk, PPV rises to 83%.

TABLE 47.3 Pretest Probability of Coronary Artery Disease according to Age, Sex, and Symptoms

Age (y)	Sex	Typical/ definite angina pectoris	Atypical/ probable angina pectoris	Nonanginal chest pain	Asymptomatic
30–39	Men	Intermediate	Intermediate	Low	Very low
	Women	Intermediate	Very low	Very low	Very low
40–49	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Low	Very low	Very low
50–59	Men	High	Intermediate	Intermediate	Low
	Women	Intermediate	Intermediate	Low	Very low
60–69	Men	High	Intermediate	Intermediate	Low
	Women	High	Intermediate	Intermediate	Low

Reproduced with permission from Gibbons RJ, Balady GJ, Bricker JT, et al. ACC/AHA 2002 guideline update for exercise testing: a report of the American College of Cardiology/American Heart Association Task Force on practice guideline (committee on exercise testing). *J Am Coll Cardiol.* 2002;40:1531–1540.

V. PATIENT PREPARATION

A. Instructions. Table 47.4 provides a typical list of instructions given to patients before testing.

B. Medications

- Before diagnostic testing, **cardiovascular drugs are withheld** at the discretion of and under the guidance of the supervising physician. This greatly increases the sensitivity of the test.
 - β -Blockers** pose a special problem. Patients taking β -blockers often do not have an adequate increase in heart rate to achieve the level of stress needed for the test. Abrupt withdrawal of β -blockers is to be discouraged because of reflex tachycardia. The best possible solution is to withdraw the β -blocker over several days before an exercise test, if the test is for diagnostic purposes. This is not always possible, however, because of time constraints or the necessity of drug therapy. In these cases, the records should reflect β -blocker use at the time of testing.
 - Digoxin** may cause problems in test interpretation. To avoid a reading that cannot be used to confirm a diagnosis, digoxin should be withheld for 2 weeks before testing.
- Patients undergoing diagnostic testing should take their **other usual medications** on the day of the test to reproduce more closely the conditions outside the exercise laboratory.

VI. EXERCISE PROTOCOLS. There are advantages and disadvantages to each exercise protocol (Table 47.5). Selection depends on the patient characteristics, the equipment available, and the familiarity and comfort of the testing personnel with the protocol.

A. An optimal protocol achieves peak workload and maximizes the sensitivity and specificity of the test.

- Workload.** An optimal protocol incorporates a **gradual increase** in the level of work, so that the patient's true peak workload can be determined. If there are large increases in workload, maximum oxygen consumption (MVO_2 max) may

TABLE 47.4 Patient Preparation

- Patients should refrain from ingesting food, alcohol, or caffeine or using tobacco products within 3 h of testing.
- Patients should be rested for the assessment, avoiding significant exertion or exercise on the day of the assessment.
- Patients should wear clothing that allows freedom of movement, including walking or running shoes, and a loose-fitting shirt with short sleeves that buttons down the front. They should not wear restrictive undergarments during the test.
- Outpatients should be warned that the evaluation may be fatiguing and that they may wish to have someone available to drive them home afterward.
- If the test is for diagnostic purposes, it may be helpful for patients to discontinue prescribed cardiovascular medication after discussion with their physician. Antianginal agents alter the hemodynamic response to exercise and significantly reduce the sensitivity of electrocardiographic changes for ischemia. Patients taking intermediate- or high-dose β -blockers should taper their medication over a 2–4-d period to minimize hyperadrenergic withdrawal responses.
- If the test is for functional purposes, patients should continue their medication regimen on their usual schedule so that the exercise responses will be consistent with responses expected during exercise training.
- Patients should bring a list of their medications with them to the assessment.

Reproduced with permission from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's guidelines for Exercise Testing and Prescription*. Baltimore, MD: Williams & Wilkins; 1995.

fall between two levels. The test is also more comfortable for the patient if the increases in workload are not large.

2. **Duration.** The optimal duration for an exercise test is **8 to 12 minutes**. Periods longer than this measure muscular endurance rather than cardiovascular fitness. Periods shorter than this do not allow adequate time for the patient to warm up and achieve maximum workloads.
3. **Stage length.** Steady-state oxygen consumption is reached after about 2 minutes of exercise at a given workload. The optimal protocol would have stage lengths of **2 to 3 minutes**.
4. **Exercise method.** Although **bicycle riding** is a better method for testing, **treadmill testing** is more commonly used in the United States.
 - a. The primary physiologic **advantage of bicycle riding** is the ability to take **direct measurements** of workload in watts, which has direct linear relation to $\dot{V}O_{2\max}$. With a **treadmill**, the examiner can only **estimate workload** because workload depends on the efficiency of walking, the weight of the patient, and the change in energy expenditure between walking and running. Other advantages of a bicycle are the stable platform that it provides for electrocardiographic and blood pressure recordings, the smaller amount of space it occupies, quieter use, and a lower initial cost of equipment.

B. Protocol options

1. Bruce protocol

- a. **Advantages.** The Bruce protocol has been widely used in the past and is often the basis of older studies; therefore, **comparisons are easier**. Because the Bruce protocol has a final stage that cannot be completed, it is a good protocol for a highly fit person.

b. Disadvantages

- (1) The main disadvantage of the Bruce protocol is the **large increments of change in workload between stages**. These large increases mean that

TABLE 47.5 Common Exercise Protocols

Functional class	O ₂ cost mL/ kg/min	MET	Treadmill protocol					
			Bruce (3-min stages mph/grade)	Cornell (2-min stages mph/grade)	Balke (2-min stages mph/grade)	Naughton (2-min stages mph/grade)	Jogger (2-min stages mph/grade)	
World-class athlete	70.0	20	—	—	—	—	—	—
	66.5	19	6.0	—	—	—	—	—
	63.0	18	—	—	—	—	6.0	20.0
	59.5	17	5.5	20	—	—	6.0	17.5
Athlete	56.0	16	5.0	18	—	—	6.0	15.0
	52.5	15	—	—	4.0	20	6.0	12.5
	49.0	14	—	4.6	17	—	6.0	10.0
	45.5	13	4.2	16	3.5	20	6.0	7.5
Fit	42.0	12	—	—	—	—	6.0	5.0
	38.5	11	—	3.8	15	20.0	5.5	2.5
	35.0	10	3.4	14	3.0	17.5	5.0	2.5
	31.5	9	—	—	3.0	15.0	—	—
Normal and 1	28.0	8	—	3.0	3.0	12.5	2.0	21.0
	24.5	7	2.5	12	3.0	10.0	7.5	—
	21.0	6	—	2.1	3.0	7.5	14.0	—
	17.5	5	1.7	10	3.0	5.0	10.5	—
2	14.0	4	—	—	3.0	2.5	7.0	—
	10.5	3	1.7	5	3.0	0	3.5	—
	7.0	2	1.7	0	—	—	0	—
	3.5	1	—	—	—	—	1.0	0

MET, metabolic equivalent; mph, miles per hour.

peak workload falls somewhere between stages for many people. This is a problem in evaluating functional capacity and may result in a lower sensitivity for the test.

- (2) The fourth stage of the Bruce protocol is an awkward stage that can be run or walked, resulting in divergent oxygen costs and workloads.
2. **Modified Bruce protocol.** Developed for less-fit persons, the modified Bruce protocol adds additional stages 0 and 1/2. These stages, at 1.7 mph (2.7 km/h) with 0% and 5% grades, respectively, provide a **lower workload for persons with poor cardiovascular fitness**. However, even these workloads may be too heavy for some debilitated patients and may result in premature fatigue.
3. **Other protocols.** Protocols superior to the Bruce protocol have been developed. These protocols have more gradual increases in workload and can be modified to suit the individual.
 - a. The **Naughton protocol** is good for older or debilitated persons and allows a gradual increase in workload.
 - b. The **Balke protocol** is good for younger, fit persons. It maintains a speed of 3, 3.5, or 4 mph (4.8, 5.6, or 6.4 km/h) and increases the grade every 2 minutes.
 - c. The **Cornell protocol** is good for a wider range of fitness levels depending on starting grade. It allows for a gradual increase in grade and speed and may be started at 0%, 5%, or 10% grade, depending on fitness level.
 - d. **Ramp protocols** are computer-driven protocols that continuously increase workload until maximum exertion is reached. This is the ultimate in continuous advancement, but steady state may not be reached at any given workload.

VII. DATA

- A. **Electrocardiographic data.** Although not the only data that should be examined, electrocardiographic changes garner the most attention in test interpretation. The **portion of the electrocardiogram (ECG) most sensitive to ischemia** is the ST segment. The pathophysiologic mechanism of the ST change is net depression caused by a current of ischemia from the affected myocardial cells. The TP segment may be useful at rest and should be used when possible; however, it shortens or disappears with exercise. Baseline electrocardiographic abnormalities that can obscure the correct diagnosis of ST changes are listed in Table 47.6.

1. ST-segment changes

- a. **Measurement of the ST segment.** There is no clear consensus as to where to measure the ST segment. Traditionally, it is measured 80 milliseconds past the J point, but some investigators suggest measuring at the J point or at the midpoint of the ST segment (using the end of the T wave or the peak of the T wave to determine the end of the segment) (Fig. 47.1A).

TABLE 47.6

Baseline Abnormalities That May Obscure Electrocardiographic Changes during Exercise

Left bundle branch block

Left ventricular hypertrophy with repolarization abnormality

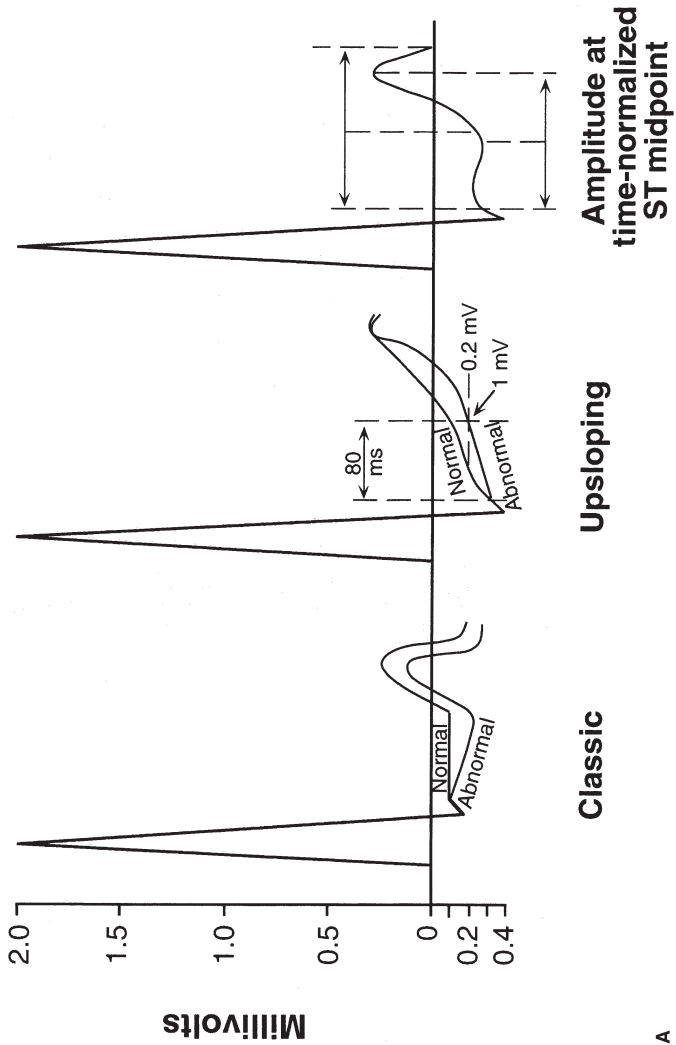
Digitalis therapy

Ventricular paced rhythm

Wolff-Parkinson-White syndrome

ST abnormality associated with supraventricular tachycardia or atrial fibrillation

ST abnormalities with mitral valve prolapse and severe anemia



A

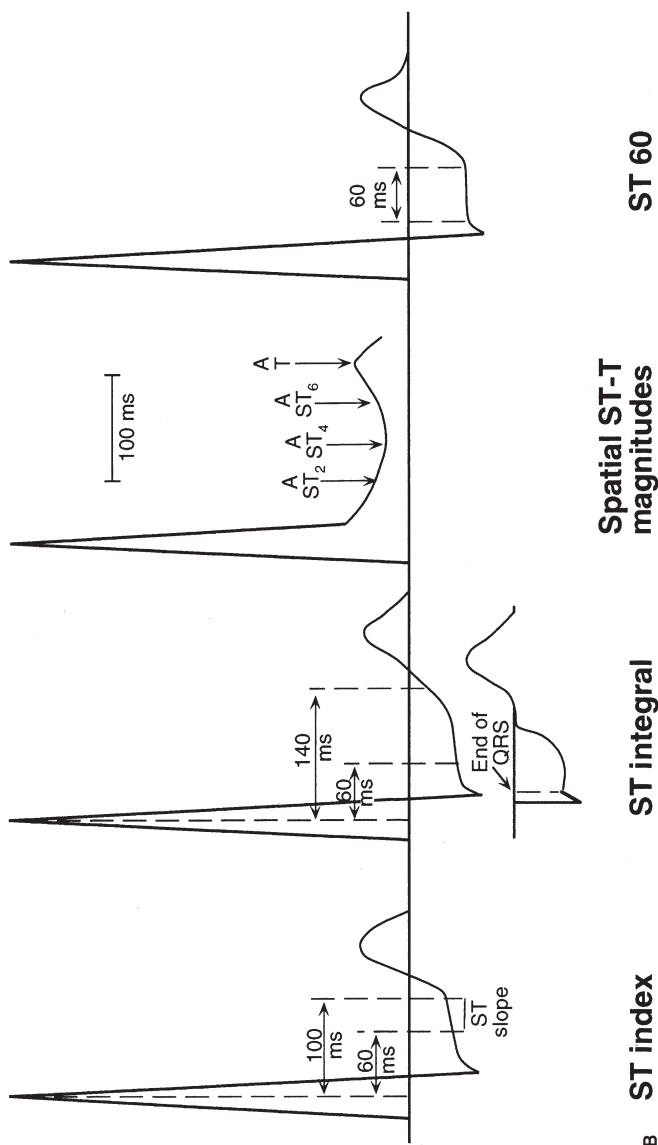


FIGURE 47.1 (A) Blomqvist recommended using the end of the T wave for measuring the midpoint of the ST segment, but Simons used the peak of the T wave. This change was made to have a more stable end point, because the end of the T wave is much more difficult to find than the peak of the T wave. (B) The ST integral, as defined by Sheffield, required that the end of the QRS complex, or J junction, be found and that the area measurement stop as soon as the ST segment crossed the isoelectric line or as the T wave began. The ST integral used by most commercial systems initiates the area at a fixed period after the R wave and then ends 80 milliseconds thereafter.

- b. **ST-segment changes** are measured from the isoelectric baseline, which can be determined from the PR interval. If the ST segment is elevated at rest, any depression that occurs with exercise is still measured from the isoelectric line; early repolarization of the ST segment at rest is normal. If, however, the ST segment is depressed at rest, any further depression should be measured from the baseline ST segment (Fig. 47.1B).
- c. **Normal response.** During exercise, there is depression of the J junction that is maximal at peak exercise and returns to baseline during recovery. This normal depression is upsloping and typically < 1 mm below the isoelectric line 80 milliseconds after the J point.
- d. **ST depression** does not localize the area of ischemia.
 - (1) ST depression of at least 1 mm that is horizontal or downsloping is abnormal, as is upsloping ST depression of at least 2.0 mm.
 - (2) Baseline ST abnormalities are less likely to represent exercise-induced myocardial ischemia, and the baseline ST depression should be subtracted from the peak ST depression.
 - (3) **Criteria that increase the probability of ischemia** are the **number of leads** involved (i.e., more leads increase the probability of ischemia), the **workload** at which the ST depression occurs (i.e., lower workload increases probability), the **angle of the slope** (i.e., a downsloping angle has a higher probability than a horizontal one), **ST-segment adjustment relative to heart rate (ST/HR index)**, the **amount of time in recovery** before normalization of the ST segment (i.e., longer recovery increases the probability), and possibly the **magnitude of the depression**. Changes in the lateral leads, particularly V_5 , are more specific than in any of the other leads. Changes in the inferior leads alone are likely to be a false-positive result.
- e. The **meaning of ST elevation** depends on the presence or absence of Q waves of prior MI.
 - (1) ST-segment elevation **with Q waves of prior MI** is a common finding among patients who have had MI. It occurs among up to 50% of patients with anterior MI and 15% of patients with previous inferior MI, and it is not caused by ischemia. The mechanism is thought to be dyskinetic myocardium or ventricular aneurysms. There may even be reciprocal ST-segment depression. Patients with more extensive Q waves have more pronounced ST elevation. These patients typically have a lower ejection fraction than those without elevated ST segment with a Q wave. These changes do not imply ischemia (although they may imply viability) and should be interpreted as normal.
 - (2) ST-segment elevation **without Q waves of prior MI** represents marked transmural myocardial ischemia. ST elevation may also indicate the location of the ischemia. This finding should be interpreted as abnormal.
- f. **ST normalization**, or the lack of ST changes during exercise, **may be a sign of ischemia**. This phenomenon occurs when ischemic ST depression and ST elevation cancel one another. This effect is rare, but it should be considered in tests of patients with no electrocardiographic changes but with a high likelihood of CAD.
- 2. **R waves may change in amplitude** during exercise. There is no diagnostic value in these changes.
- 3. **T-wave and U-wave changes**
 - a. The **T wave** normally decreases gradually in early exercise and begins to increase in amplitude at maximal exercise. One minute into recovery, the T wave should be back to baseline. T-wave **inversion is not a specific marker of ischemia** and may occur normally.

TABLE 47.7 Absolute and Relative Indications for Termination of an Exercise Test**Absolute indications**

Acute myocardial infarction or suspicion of myocardial infarction
 Onset of moderate to severe angina or increasing anginal pain
 Drop in systolic blood pressure with increasing workload accompanied by signs or symptoms or drop below resting pressure
 Serious arrhythmias (e.g., second- or third-degree atrioventricular block, sustained ventricular tachycardia or increasing premature ventricular contractions, and atrial fibrillation with fast ventricular response)
 Signs of poor perfusion, including pallor, cyanosis, or cold and clammy skin
 Unusual or severe shortness of breath
 Central nervous system symptoms, including ataxia, vertigo, visual or gait problems, or confusion
 Technical inability to monitor the electrocardiogram
 Patient's request

Relative indications

Pronounced electrocardiographic changes from baseline > 2 mm of horizontal or downsloping ST-segment depression or > 2 mm of ST-segment elevation except in aVR
 Any chest pain that is increasing
 Physical or oral manifestations of severe fatigue or shortness of breath
 Wheezing
 Leg cramps or intermittent claudication (grade 3 on 4-point scale)
 Hypertensive response (systolic blood pressure > 260 mm Hg and diastolic blood pressure > 115 mm Hg)
 Less serious arrhythmias such as supraventricular tachycardia
 Exercise-induced bundle branch block that cannot be differentiated from ventricular tachycardia
 General appearance

Adapted from Kenney WL, Humphrey RH, Bryant CX, eds. *ACSM's Guidelines for Exercise Testing and Prescription*. 5th ed. Baltimore, Md: Williams & Wilkins; 1995 and from Fletcher GF, Blair SN, et al. statement on exercise. Benefits and recommendations for physical activity programs for all Americans. A statement for health professionals by the Committee on Exercise and Cardiac Rehabilitation of the Council on Clinical Cardiology, American Heart Association. *Circulation*. 1992;86:340–344

- b. If the U wave is upright at baseline, **U-wave inversion** may be associated with ischemia, left ventricular hypertrophy, and valvular disease.
4. **Arrhythmias.** Table 47.7 lists abnormal arrhythmias that may occur during exercise. Ectopic atrial and ventricular beats during exercise are not predictive of outcome, but ventricular ectopy during recovery may be associated with worse outcome. Sustained ventricular tachycardia and ventricular fibrillation are abnormal but occur rarely.
5. **Time to resolution of changes.** The longer into recovery that it takes for electrocardiographic changes to resolve, the higher is the probability that they are important. Rapid recovery (< 1 min) indicates less likelihood of disease and that disease if present is less severe.

6. Bundle branch block or conduction delay. Exercise-induced left bundle branch block is predictive of a worse outcome.
- B. **Age-predicted maximum heart rate (APMHR).** Many formulas have been developed to predict maximum heart rate (MHR). These formulas are generated by measuring the MHR in a sample population and plotting a regression line against various factors that may affect heart rate. There is a great deal of scatter on either side of the regression line, and the fit of the line seldom reaches an r value > 0.9 . Because MHR decreases with age, most equations incorporate age into the estimation. The two most common formulas are as follows:

$$\text{APMHR} = 220 - \text{age}$$

$$\text{APMHR} = 200 - \frac{1}{2} \text{ age}$$

- The APMHR may be much lower or much higher than a person's actual measured MHR. **Heart rate should not be used as an indicator of maximal exertion or in the decision to terminate testing, except in a submaximal test.** If MHR does not exceed 85% of APMHR during testing and there are no substantial electrocardiographic changes, the test is usually read as nondiagnostic. If there are substantial electrocardiographic changes, the test is read as abnormal, regardless of the heart rate achieved.
- C. **Rating of perceived exertion (RPE)** is a better marker of maximal level of exertion.
 1. A useful indicator of percentage of maximum workload achieved is the **RPE scale**. This is a subjective scale used to rate how much effort the subject feels he or she is expending during an exercise test. The subject should be advised to rate how he or she feels overall and not according to an individual element such as leg fatigue. Although subjective, the scale has been shown to be reproducible, and maximum ratings correspond well with maximum exertion.
 - a. The **Borg scale** is used most often. The original scale ranges from 6 to 20, which is meant to correspond to a heart rate increase from 60 to 200 beats/min during exercise.
 - b. The **modified Borg scale** ranges from 0 to 10. The scale includes word anchors, which are important for an accurate assessment of work level. The scales are not linear, and at higher workloads, the changes in RPE are closer together.
 2. A maximal level of exertion is marked by a score > 18 (Borg scale) or 9 (modified Borg scale), respiratory quotient > 1.1 (if carbon dioxide exchange is monitored), and overall patient appearance.
 - D. In addition to electrocardiographic monitoring, **blood pressure monitoring** is an important aspect of the exercise test for safety and for the diagnosis of CAD. It should be checked in each walking stage. It may not be practical to check blood pressure while the subject is running.
 1. **Systolic blood pressure** (SBP) normally rises during exercise. A **failure of SBP to rise** with increasing workload or a drop in SBP usually indicates the presence of CAD and is an indication to **terminate testing**.
 2. **Diastolic blood pressure** decreases with exercise and may be audible down to 0 during vigorous activity. Unlike SBP, diastolic blood pressure is not useful in diagnosis or safety monitoring.
 - E. **Symptoms.** The presence or absence of symptoms and their change over time are included in the final report.
 - F. **Functional capacity.** Functional testing is a powerful marker for prognosis. Persons who achieve > 6 metabolic equivalents (METs) of workload have a significantly lower mortality rate than those who do not achieve this workload, regardless of electrocardiographic changes. On the basis of age and workload achieved, functional capacity can be divided into five classifications (Table 47.8). Among 3,400 patients with no history of diagnosed CAD undergoing exercise testing at the Cleveland Clinic, those with average or better classifications had a 2.5-year mortality of $< 2\%$ compared with 6%

TABLE 47.8 Functional Capacity Classifications by Age and Sex

Age (y)	Low ^a	Fair	Average	Good	High
Women					
20–29	< 7.5	8–10.3	10.3–12.5	12.5–16	> 16
30–39	< 7	7–9	9–11	11–15	> 15
40–49	< 6	6–8	8–10	10–14	> 14
50–59	< 5	5–7	7–9	9–13	> 13
60–69	< 4.5	4.5–6	6–8	8–11.5	> 11.5
Men					
20–29	< 8	8–11	11–14	14–17	> 17
30–39	< 7.5	7.5–10	10–12.5	12.5–16	> 16
40–49	< 7	7–8.5	8.5–11.5	11.5–15	> 15
50–59	< 6	6–8	8–11	11–14	> 14
60–69	< 5.5	5.5–7	7–9.5	9.5–13	> 13

^aFunctional capacities are given in metabolic equivalents.

and 14% for those who were in the fair and poor groups, respectively. The adjusted relative risk for fair or poor functional capacity in this population was almost 4.

VIII. TERMINATION OF EXERCISE TESTING. The American Heart Association (AHA) and American College of Sports Medicine (ACSM) have developed very similar indications for exercise termination (Table 47.7). The decision when to terminate a test ultimately relies on the expertise and judgment of those performing the test.

A. Absolute indications are all serious findings. A drop in SBP with increasing workload is a particularly ominous sign and usually, but not always, indicates the presence of severe CAD.

B. Relative indications for termination of testing are findings that should increase the level of concern and vigilance among those administering the test and possibly cause cessation of testing. Relative indications for termination rely heavily on the judgment of the personnel performing the test, and the decision to continue the test should not be made lightly (Table 47.7).

C. Indications for termination of submaximal exercise testing include any one of the following end points:

- (1) Signs or symptoms of ischemia
- (2) Achievement of a workload of 6 METs
- (3) Eighty-five percent of the APMHR
- (4) Heart rate of 110 beats/min for a patient taking β -blockers
- (5) A score on the Borg RPE of 17 or modified Borg RPE of 7

D. Postexercise recovery

1. In **all routine exercise tests, a cool-down period** adds safety to the test. The length of the cool-down period may vary from 30 seconds to several minutes, depending on the person. A general rule is to allow enough time for the heart rate to drop to < 110 beats/min. A shorter cool-down period increases the sensitivity of exercise ECG because of increased venous return; resuming the supine position leads to increased wall stress. This same mechanism also increases the risk of testing.

2. The exception to observing a cool-down period may be made for exercise echocardiography, in which it is important to image the subject when he or she is as close as possible to MHR.

IX. INTERPRETATION OF DATA. An experienced clinician must interpret an exercise electrocardiographic test. Although the terms *positive* and *negative* are often used, these terms do not accurately describe the results of an exercise electrocardiographic test and should be avoided. The information to include in an exercise electrocardiographic report is listed in Table 47.9.

A. Exercise electrocardiographic test results can be normal, abnormal, normal except for, or nondiagnostic (Table 47.10). Nondiagnostic tests are those in which the subject does not achieve 85% of APMHR and has no abnormal electrocardiographic changes or in which baseline electrocardiographic changes are present that obscure ST changes (Table 47.6).

B. Prognosis

1. The **Duke nomogram** (Fig. 47.2) is a simple chart that factors in ST-segment deviation, amount of angina during exercise, and exercise capacity to give an estimate of a 5-year survival and average annual mortality. This nomogram was derived by means of regression analysis and can be a useful tool in determining prognosis and the degree of aggressiveness needed in treating a patient. The **Duke treadmill score (DTS)** is a numeric form of the nomogram and has been validated in several studies as an important predictor of mortality:

$$\text{DTS} = \text{duration of exercise (in minutes)} - (5 \times \text{maximal ST-segment deviation}) - (4 \times \text{angina score})$$

TABLE 47.9 Elements of Conclusion Section of a Modern Exercise Test Report

Exercise protocol used, duration of exercise, peak treadmill speed and grade, maximum heart rate and percentage of age-predicted maximum heart rate achieved, resting and peak blood pressure, and symptoms
Negative/positive/equivocal standard ST-segment response to exercise
"The ST/HR index of ≤ 1.6 $\mu\text{V}/\text{beats}/\text{min}$ is consistent with the absence of obstructive coronary disease and makes anatomically, functionally, and prognostically important coronary disease unlikely"; "The ST/HR index > 1.6 $\mu\text{V}/\text{beats}/\text{min}$ is consistent with the presence of obstructive coronary disease and predicts increased cardiovascular risk
The estimated functional capacity of (x METs) predicts (high/low) risk of all-cause mortality
The Duke treadmill score of (x) predicts a cardiac mortality of ($x\%$) per year over the next 5 y. This implies a (low/intermediate/high) risk
The chronotropic response index of ($0.xx$) predicts an (increased/decreased) risk of death compared with the Duke treadmill score. For patients not on β -blockers, a value ≤ 0.80 raises concerns; for patients on β -blockers, a value ≤ 0.62 is abnormal
The heart rate recovery of (x beats/min) further predicts an (increased/decreased) risk of death
The presence/absence of frequent ventricular ectopy during recovery further increases/decreases predicted risk of death

Adapted from Kligfield P, Lauer MS. Exercise electrocardiogram testing: beyond the ST segment. *Circulation*. 2006;114:2070–2082.

TABLE 47.10

Guidelines for Interpretation of Results of Exercise Electrocardiography

Variable	Normal	Normal except for	Abnormal
Symptoms	Neuromuscular chest pain Fatigue, shortness of breath, and leg or joint pain	Angina as an isolated finding Atypical angina Chest discomfort of questionable causation Claudication Dizziness and lightheadedness Other noteworthy symptoms	Syncope Angina when associated with ST- or T-wave changes, including borderline Angina when associated with exercise hypotension
Blood pressure response (mm Hg)	SBP increases > 10 but is < 230 at peak DBP increases ≤ 10 but is < 120 at peak DBP stays the same or decreases DBP increases ≥ 12 from rest but peak is < 100	SBP ≥ 230 at peak exercise DBP ≥ 120 at peak exercise DBP increases ≥ 12 from rest if peak is ≥ 100	Any drop in SBP as exercise intensity increases
Arrhythmias	Occasional PVCs PACs Frequent PACs or PVCs at rest that abate during exercise	Paroxysmal SVT Increased frequency of PVCs or couplets during exercise Isolated run of nonsustained VT	Sustained SVTs, AF, atrial flutter, or junctional rhythm Nonsustained VT Second- or third-degree AV block

(Continued)

TABLE 47.10

Guidelines for Interpretation of Results of Exercise Electrocardiography (Continued)

Variable	Normal	Normal except for	Abnormal
	Chronic AF, atrial flutter	Ventricular couplets Paroxysmal escape rhythms	AV dissociation Exercise induced before excitation Idioventricular rhythm <i>Very abnormal</i> Sustained VT (≥ 30 s) VF/cardiac arrest Asystole
ST segments	< 1.0 mm ST depression or elevation	Borderline ST changes (0.5–0.9 mm ST depression) ST elevation in leads in area of prior MI T-wave inversion Pseudonormalization of resting T-wave abnormalities	≥ 1.0 mm H or D ST depression ≥ 1.5 mm U ST depression ≥ 1.0 mm U ST depression if associated with anginal symptoms ≥ 1.0 mm ST elevation in leads without Q waves or not over a prior MI <i>Very abnormal</i> ≥ 2.0 mm H or D ST depression ≥ 2.5 mm U ST depression ≥ 2.0 mm ST elevation in leads without Q waves or not over a prior MI Inability to achieve 3 MET workload
Functional capacity	Normal or mildly impaired exercise tolerance	Low exercise tolerance	

AF, atrial fibrillation; AV, atrioventricular; D, downsloping; DBP, diastolic blood pressure; H, horizontal; MET, metabolic equivalent; MI, myocardial infarction; PAC, premature atrial contraction; PVC, premature ventricular contraction; SBP, systolic blood pressure; SVT, supraventricular tachycardia; U, upsloping; VF, ventricular fibrillation; VT, ventricular tachycardia.

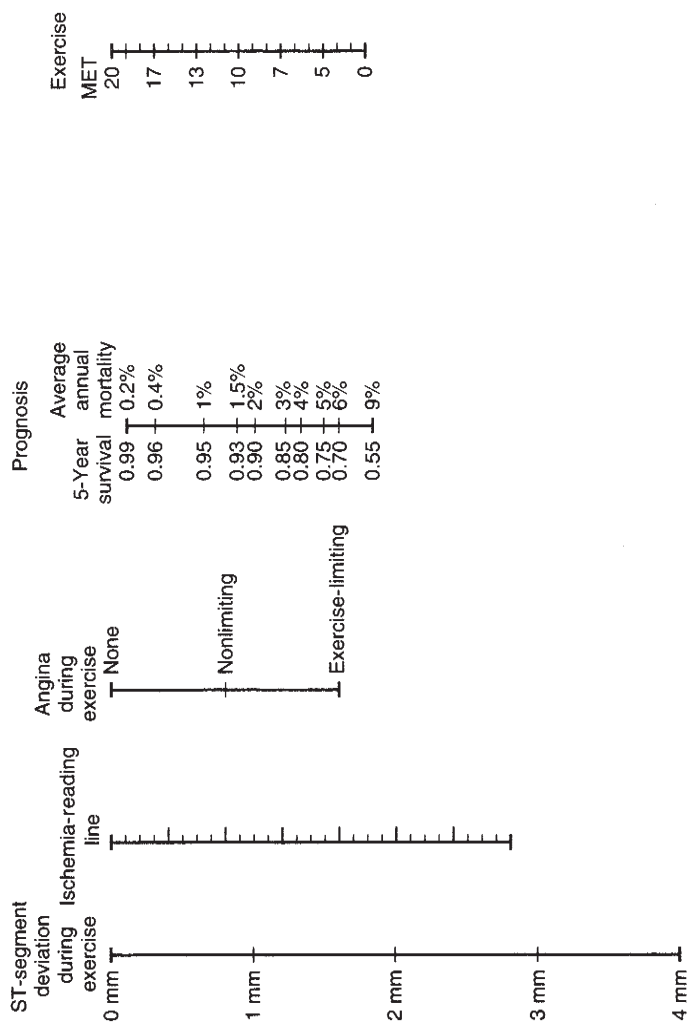


FIGURE 47.2 Duke nomogram for estimation of the prognosis. MET, metabolic equivalent.

In the previous equation, 0 = no angina, 1 = non-test-limiting angina, and 2 = exercise-limiting angina.

Low risk: DTS $\geq +5$

Intermediate risk: DTS -10 to $< +5$

High risk: DTS < -10

2. The **heart rate recovery**, defined as the difference in heart rate at peak exercise and at 1 minute after cessation of exercise, has important prognostic significance. A heart rate recovery of 12 beats/min or less is considered abnormal during an upright cool-down period. For patients assuming an immediate supine position, such as during exercise echocardiography, a value of < 18 beats/min is considered abnormal.
3. The **chronotropic response index (CRI)** is a measure of MHR in relation to chronotropic reserve. A normal response is defined as a CRI of > 0.8 (0.62 for patients on β -blockers):

$$\text{CRI} = \frac{\text{peak HR} - \text{resting HR}}{\text{APMHR} - \text{resting HR}}$$

4. **Ventricular ectopy in recovery** from exercise, including frequent ventricular ectopics ($> 7/\text{min}$), couplets, bigeminy, trigeminy, ventricular tachycardia, and ventricular fibrillation, has been shown to be predictive of all-cause mortality. These findings in recovery are a better predictor of death than ventricular ectopy during exercise.
5. A published nomogram (1) for patients with suspected CAD and a normal ECG undergoing exercise treadmill testing demonstrates how a simple combination of clinical and stress-testing variables can be used to predict mortality.

X. POTENTIAL COMPLICATIONS. Complications of exercise electrocardiographic testing are rare, but they do occur (Table 47.11). Exercise testing of healthy persons without CAD rarely results in cardiac complications, which are most likely to occur among persons with underlying CAD. Several researchers have looked at large numbers of unselected persons involved in various activities to determine risk.

A. Cardiac arrest

1. For the **general population**, there is approximately 1 cardiac arrest per 565,000 person-hours of exercise.
2. Among **persons with known CAD**, there is an estimated 1 arrest per 59,000 person-hours of vigorous activity. Exercise testing may precipitate acute coronary symptoms. Acute MI has been reported in approximately 1.4 per 10,000 exercise tests.
3. Among **persons at low risk** for CAD, however, the risk for cardiac arrest during exercise testing is much lower. In one study, no complications occurred in 380,000 exercise tests of young persons with presumably no heart disease.

B. Arrhythmic complications are a potential hazard of exercise testing (Table 47.10). Arrhythmias are more likely among persons with a history of arrhythmia. In this population, they occur in 9% of tests compared with an overall incidence of 0.1%.

1. **Atrial fibrillation** is the most common arrhythmia that occurs during testing, occurring in 9.5 per 10,000 tests.
2. **Ventricular tachycardia** is less common, occurring in 5.8 per 10,000 tests.
3. **Ventricular fibrillation** is even less common, occurring 0.67 times per 10,000 tests.

C. Deaths during exercise testing are exceedingly rare among well-monitored patients, but may occur in 1 of 25,000 tests. If death occurs, it is usually caused by sudden cardiac death or MI.

TABLE 47.11 Potential Medical Complications of Exercise Electrocardiographic Testings**Cardiovascular complications**

Cardiac arrest
Ischemia
 Angina
 Myocardial infarction
Arrhythmias
 Supraventricular tachycardia
 Atrial fibrillation
 Ventricular tachycardia
 Ventricular fibrillation
Bradyarrhythmias
 Bundle branch blocks
 Atrioventricular nodal blocks
Congestive heart failure
Hypertension
Hypotension
Aneurysm rupture

Underlying medical conditions predisposing to increased complications

Hypertrophic cardiomyopathy
Coronary artery anomalies
Idiopathic left ventricular hypertrophy
Marfan's syndrome
Aortic stenosis
Right ventricular dysplasia
Congenital heart defects
Myocarditis
Pericarditis
Amyloidosis
Sarcoidosis
Long QT syndrome
Sickle cell trait
Sudden death

Pulmonary complications

Exercise-induced asthma
Bronchospasm
Pneumothorax

(Continued)

TABLE 47.11 Potential Medical Complications of Exercise Electrocardiographic Testing (*Continued*)

Exercise-induced anaphylaxis

Exacerbation of underlying pulmonary disease

Gastrointestinal complications

Vomiting

Cramps

Diarrhea

Neurologic complications

Dizziness

Syncope (fainting)

Cerebrovascular accident (stroke)

Musculoskeletal complications

Mechanical injuries

Back injuries

Joint pain or injury

Muscle cramps or spasms

Exacerbation of musculoskeletal disease

ACKNOWLEDGMENTS: *The author thanks Drs. Christopher Cole, Julie Huang, and Einar Gorodeski for their contributions to earlier editions of this chapter.*

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Nuclear Cardiac Imaging

I. INTRODUCTION. Nuclear cardiology has an integral role in the noninvasive detection of coronary artery disease (CAD), assessment of myocardial viability, and stratification of risk. It imparts improved sensitivity and specificity over standard exercise stress testing. For example, the average sensitivity and specificity of single-photon emission computed tomography (SPECT) with technetium 99m have been reported to be 90% and 74%, respectively—though the exact performance characteristics depend on the prevalence of the disease in the population being studied. Nuclear imaging can provide functional and prognostic information that is quantifiable, reproducible, and readily obtainable in diverse patient populations.

II. INDICATIONS (Table 48.1)

- A. Diagnosis of CAD.** Nuclear perfusion studies are performed to establish noninvasively the diagnosis of CAD in the following situations: history of **stable angina**; **chest pain of unclear causation**; **unstable angina** after stabilization; **abnormal exercise test result** without symptoms; **risk stratification** in the setting of multiple factors thought to confer a high likelihood of subclinical CAD; scheduled standard exercise testing in the setting of an **abnormal electrocardiogram** (ECG; due to left ventricular hypertrophy with associated repolarization changes, ST depression >1 mm, manifest pre-excitation pattern on ECG, digoxin use, left bundle branch block, or ventricular-paced rhythm); and previously **nondiagnostic graded exercise test**.
- B. Assessment of the physiologic importance of known CAD.** Perfusion imaging can assist in the determination of the functional significance of a coronary stenosis that is in the “moderate-to-severe” (50% to 70%) range on angiographic evaluation. It can therefore be useful to evaluate a specific coronary lesion before proceeding to percutaneous intervention. This remains an accepted indication for nuclear perfusion imaging, although its use for this purpose is being supplanted by other modalities that can assess the functional significance of coronary lesions at the time of angiography (e.g., fractional flow reserve).
- C. Assessment after therapeutic intervention.** In the past, perfusion imaging was often performed as a routine follow-up procedure after percutaneous intervention and coronary artery bypass grafting (CABG). More recent recommendations on appropriate use of this modality suggest that routine screening in *asymptomatic* patients who have been successfully revascularized by either method is not necessarily warranted, except in the evaluation of patients more than 5 years after CABG. On the other hand, radionuclide perfusion imaging is certainly appropriate in patients who have undergone prior revascularization and are presenting with recurrent symptoms consistent with coronary ischemia.
- D. Risk stratification.** With nuclear imaging, it is possible to stratify risk among patients with stable angina or unstable angina, those who have had myocardial infarction (MI), and those about to undergo noncardiac operations.

Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCT/SCMR/ SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging

Patient group	Condition	Imaging technique
ER patient with chest pain	For risk stratification in pt with <i>possible</i> ACS. Initial serum markers and enzymes. ECG is nondiagnostic. For CAD diagnosis in pt with <i>possible</i> ACS and nondiagnostic ECG. Negative serum markers and enzymes or normal rest perfusion scan. Assessment of LV function.	Rest perfusion imaging (with ECG gating, if possible). Same-day rest/stress (ECG-gated) myocardial perfusion imaging.
Acute MI/unstable angina	Assessment of LV function.	Rest myocardial perfusion imaging with ECG gating (rest gated radionuclide angiography is alternative option).
ST-elevation MI	Measurement of infarct size and residual viable myocardium, in an unvascularized asymptomatic stable patient after completion of the infarct. Thrombolysis without coronary angiogram, to identify inducible ischemia and myocardium at risk.	Rest myocardial perfusion imaging with ECG gating or with stress perfusion imaging with ECG gating.
Non-ST-elevation MI/unstable angina	In an unvascularized stable asymptomatic patient after completion of the infarct, to determine the extent and severity of inducible ischemia, either in the distribution of the “culprit” vessel or in remote myocardium. In individuals whose angina is stabilized on medical therapy or in whom the diagnosis is uncertain, to identify the extent and severity of inducible ischemia. To assess the functional significance of a coronary stenosis on angiography.	Rest and stress myocardial perfusion imaging, with ECG gating whenever possible. Rest and stress myocardial perfusion imaging, with ECG gating whenever possible. Rest and stress myocardial perfusion imaging, with ECG gating whenever possible. Rest and stress myocardial perfusion imaging, with ECG gating whenever possible.

(Continued)

TABLE 48.1

Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCT/SCMR/ SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (Continued)

Patient group	Condition	Imaging technique
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease <i>and</i> able to exercise to 85% MPRH or more	Those with pre-excitation, LVH, on digoxin, or >1 mm ST-segment depression on resting ECG.	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
	Individuals with left bundle branch block or ventricular-paced rhythm.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	Patients with an intermediate- or high-risk Duke treadmill score.	Rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
	In an individual with prior abnormal myocardial perfusion scan and new or worsening symptoms.	Repeat rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible.
CAD diagnosis in an individual with an intermediate probability of disease and/or risk stratification in someone with an intermediate or high likelihood of disease <i>and not</i> able to exercise	To identify the extent, severity, and location of inducible ischemia.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
Detection of CAD in patients with ventricular tachycardia	Patients without known CAD or ischemic equivalent.	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible.
Detection of CAD in patients with syncope.	Patients with intermediate and high risk for CHD and no ischemic equivalent.	Rest and stress myocardial perfusion imaging, preferably exercise stress, with ECG gating whenever possible.

(Continued)

Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCT/SCMR/ SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (Continued)

Patient group	Condition	Imaging technique
Prior to intermediate- and high-risk noncardiac surgery	Initial diagnosis of CAD in those with at least one clinical risk factor for adverse perioperative CV events, and poor (<4 METS) or unknown functional capacity.	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible or In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
	In individuals with established or suspected CAD and poor (<4 METS) or unknown functional capacity.	In those able to exercise, rest and exercise stress myocardial perfusion imaging, with ECG gating whenever possible or In those unable to exercise, rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible
	Diagnosis of CAD in patients with left bundle branch block or ventricular-paced rhythm and at least one risk factor for adverse perioperative CV events.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
	In suspected or established CAD, prognostic assessment of those with left bundle branch block or ventricular-paced rhythm on rest ECG.	Rest and vasodilator stress myocardial perfusion imaging, with ECG gating whenever possible.
Equivocal SPECT myocardial perfusion scan	Clinically indicated SPECT perfusion study is equivocal for CAD diagnosis or risk stratification purposes.	Rest and adenosine or dipyridamole stress PET myocardial perfusion study.

(Continued)

TABLE 48.1 Appropriate Indications for Myocardial Perfusion Imaging—Based on the ACCF/ASNC/ACR/AHA/ASE/SCT/SCMR/ SNM 2009 Appropriate Use Criteria for Cardiac Radionuclide Imaging (Continued)		
Patient group	Condition	Imaging technique
CAD patient with systolic dysfunction and CHF, with little or no angina	Prediction of improvement in regional/global LV function following revascularization.	Stress/redistribution/reinjection thallium 201 SPECT perfusion imaging
		or
		Rest/redistribution SPECT perfusion imaging
	Prediction of improvement in natural history following revascularization.	or
		Myocardial perfusion plus FDG PET metabolic imaging
		or
		Resting sestamibi SPECT perfusion imaging.
		Stress/redistribution/reinjection thallium 201 SPECT perfusion imaging
		or
		Rest/redistribution thallium 201 SPECT perfusion imaging
		or
		Myocardial perfusion plus FDG PET metabolic imaging.

ACS, acute coronary syndrome; CAD, coronary artery disease; CHF, congestive heart failure; CV, cardiovascular; ECG, electrocardiogram; ER, emergency room; FDG, [18F]fluoro-2-deoxyglucose; LV, left ventricular; LVH, left ventricular hypertrophy; MI, myocardial infarction; MPHR, maximal age-predicted heart rate; PET, positron emission tomography; pt, patient; SPECT, single-photon emission computed tomography.

- E. **Identification of prior MI** among patients with angiographically normal coronary arteries is afforded by nuclear imaging.
- F. **Assessment of left ventricular (LV) function.** Although nuclear imaging is used less often for this purpose than in the past—due to the desire to reduce patients' radiation exposure when possible—gated blood pool imaging remains an accurate method of determining the ejection fraction.

III. CONTRAINDICATIONS. In addition to standard contraindications to exercise stress testing, specific considerations apply uniquely to nuclear imaging in general and the subgroup of dipyridamole stress perfusion studies.

- A. **General contraindications to nuclear studies.** Nuclear imaging is contraindicated for patients who have had **iodine 131 therapy** within 12 weeks; **technetium 99m studies** within 48 hours, including bone, lung, multigated acquisition (MUGA), liver, tagged red blood cell (to evaluate gastrointestinal bleeding), and renal scans; **indium 111 scans** within 30 days; **gallium 67 scans** within 30 days; and **oral intake** within 4 hours (except for water).
- B. **Contraindications to dipyridamole, adenosine, or regadenoson** administration include allergy to any of these agents, allergy to aminophylline, ongoing theophylline therapy (must be discontinued for 36 hours), history of uncontrolled asthma or reactive airway disease, significant atrioventricular nodal block, and caffeine consumption within 12 to 24 hours.

IV. EQUIPMENT. The most basic tool in nuclear imaging is the **gamma or scintillation camera**, which is used to detect gamma rays (i.e., x-ray photons) produced by the chosen radionuclide. Three types of gamma camera exist.

- A. A **single-crystal camera** consists of one large sodium iodide crystal. Other essential elements of this camera include the **collimator**, a lead device that screens out background or scattered photons, and the **photomultiplier**, an electronic processor that translates photon interactions with the crystal into electric energy.
 - 1. Electric signals from the photomultiplier are processed by the **pulse height analyzer** before reaching a final form. Only signals in a specified energy range are incorporated into the interpreted images. The range recognized by the pulse height analyzer is adjustable and is established on the basis of the radiopharmaceutical used.
 - 2. **Digitalization** of the single-crystal camera has greatly enhanced its performance.
- B. A **multicrystal camera** works with an array of crystals with increased count detection capability. Because of the availability of an individual crystal to detect scintillation at any given time, this type of camera can be used to detect many more counts than can a single-crystal camera.
- C. In the case of positron emission tomography (PET) scanning, a **positron camera** is a gamma camera used to detect the photon products of positron annihilation. Interaction between a positron and an electron causes annihilation, with the generation of two high-energy photons (511 keV) that travel in opposite directions.
 - 1. An array of multiple concentric rings of crystals constitute a positron camera. Each crystal is linked optically to multiple photomultipliers. The crystals are oriented in diametric pairs in such a way that each pair of crystals must be struck simultaneously by annihilation photons to record activity. Background interference and stray photon energy are automatically accounted for, and artifact is limited.
 - 2. Most positron cameras contain **bismuth germanate** for annihilation photon detection. The clinical utility and radiopharmaceuticals for PET are discussed in Section X.

V. MECHANICS AND TECHNIQUES

- A. **Image acquisition.** Basic perfusion imaging can be performed by means of **planar** and **tomographic** techniques. The tomographic, or SPECT, method is the most commonly used today.

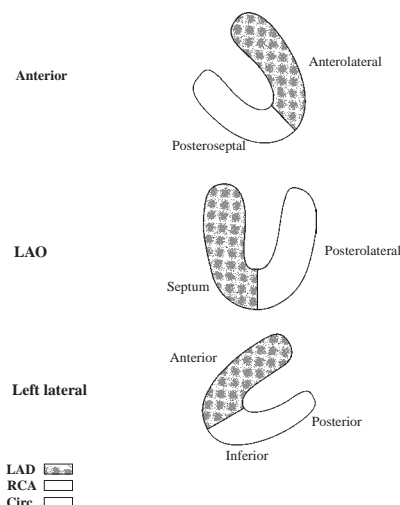


FIGURE 48.1 Standard planar views and vascular territories. Circ: circumflex artery; LAO, left anterior oblique; LAD: left anterior descending artery; RCA: right coronary artery.

1. **Planar images** are acquired in three views: **anterior**, **left anterior oblique (LAO)**, and **steep LAO** or **left lateral (LLAT) orientation** (Fig. 48.1). The patient is supine for anterior and LAO views but is placed in the lateral decubitus position for LLAT image acquisition. Although it allows examination of specific myocardial segments, planar imaging superimposes vascular distributions and therefore can compromise the ability to implicate a specific vascular supply when a defect is present. For example, normally perfused myocardial segments may overlap perfusion defects in a separate distribution.
2. Using **SPECT**, a series of planar images are usually obtained over a 180° arc to reconstruct a three-dimensional representation of the heart. The arc typically extends from the 45° right anterior oblique plane to the 45° left posterior oblique plane, with the patient in the supine position.
 - a. Three orientations are analyzed in the final representation: **short axis**, **vertical long axis**, and **horizontal long axis**. A computer-generated display, the **polar map**, is also analyzed as a quantifiable representation of count density.
 - b. Unlike planar imaging, **SPECT** can be used to **separate vascular territories** and improve image interpretation. SPECT, however, also **increases the time needed** for image acquisition and requires close attention to quality control issues.
- B. **Radiopharmaceuticals** available for nuclear imaging include thallium 201, technetium 99m, and several positron imaging agents. Each possesses specific energy characteristics, kinetic profiles, and biodistribution (see below as well as Table 48.2 and Section X for further details).
 1. **Thallium 201**
 - a. **General characteristics.** Thallium 201 (i.e., thallous chloride) is a metallic element in group IIIA of the periodic table; it is produced in a cyclotron. Thallium emits gamma rays at an energy range of 69 to 83 keV and has a **half-life of 73 hours**. The biologic activity of this element is very similar to that of potassium; the ionic radii of the two elements are virtually identical. Thallium is actively transported into cells by the sodium–potassium adenosine triphosphatase (Na-K ATPase) pump.

TABLE 48.2 Characteristics of Common Perfusion Agents

Attribute	Thallium 201	Technetium 99m sestamibi	Technetium 99m tetrofosmin	Technetium 99m tetrofosmin
Energy (keV)	69–83	140	140	140
Dose (mCi)	2.5–3.5	20–30	20–30	20–30
Half-life (h)	74	6	6	6
Cyclotron required	Yes	No	No	No
Perfusion imaging	Yes	Yes	Yes	Yes
Viability evaluation	Yes	Yes	Yes?	No
Redistribution	Yes	Yes (minimal)	Yes (minimal)	Yes
Gating (electrocardiogram)	No	Yes	Yes	No

- b. Kinetics.** Approximately 5% of the administered dose of thallium 201 is distributed to the myocardium, proportionate to the blood flow delivered to the coronary circulation. Almost 85% of the thallium 201 is extracted by myocytes in the first pass.

- (1) The **initial uptake** of thallium 201 by myocardium is directly related to regional blood flow. The myocardial extraction of thallium 201, however, increases at low flow rates (<10% of basal) and decreases at high flow rates (more than twice the basal rate).
- (2) **Washout.** After initial uptake into myocytes, a state of continuous exchange across the cell membrane occurs. The distribution of this radio-tracer changes after administration, and thallium 201 washes out from the myocytes, a process called **redistribution**. Thallium 201 washout generally approaches 30% at 2 to 2.5 hours after injection.
- (3) **Ischemic myocardium.** Uptake of thallium 201 in ischemic myocardium is lower than uptake in nonischemic segments. Washout time from ischemic zones is slower than that from nonischemic zones.
- (4) Over time, counts become equal in the ischemic and nonischemic regions (or thallium 201 concentration may increase in ischemic regions) so that thallium 201 concentrations in these disparate areas approach one another. This disparity is taken advantage of during thallium 201 viability imaging (described below).

2. Technetium 99m-labeled agents

- a. General characteristics.** Technetium 99m is a radiopharmaceutical that can be produced on-site in molybdenum 99–technetium 99m generators. It possesses several ideal imaging characteristics.
- (1) Technetium 99m has a **half-life of 6 hours** and emits gamma rays with a single photopeak of 140 keV.
 - (2) Technetium 99m-labeled **perfusion agents** include ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin, and ^{99m}Tc-teboroxime. Although ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin have similar properties, ^{99m}Tc-tetrofosmin may be less sensitive at detecting ischemic changes and its use for viability detection is less well validated.
- b. Kinetics.** After administration of ^{99m}Tc-sestamibi, approximately 40% to 60% of the agent is extracted by the myocardium. Initial uptake of the agent

is proportional to regional myocardial blood flow, and it is bound to the inner mitochondrial membrane. ^{99m}Tc -tetrofosmin has similar pharmacokinetics to ^{99m}Tc -sestamibi.

Myocardial washout of ^{99m}Tc -sestamibi and ^{99m}Tc -tetrofosmin is very slow, and little redistribution occurs. The absence of redistribution requires two separate injections of the agent, at **rest** and at **peak exercise** (or with pharmacologic stress). This can be performed with a same-day or 2-day protocol.

VI. IMAGING PROTOCOLS

A. Thallium 201

1. **General features.** Stress imaging with thallium 201 involves **injection at peak exercise** (or with pharmacologic stress) and **immediate imaging**, followed by **redistribution images** 3 to 4 hours after injection.
 - a. Because of the long half-life of thallium 201 (i.e., 73 hours), to reduce the total radiation exposure to the patient, limited amounts are administered. Although a single injection is typically used because of the redistribution phenomenon, a second injection may be given to enhance the filling of reversible defects.
 - b. The low energy range of thallium 201 is marginal for imaging with the gamma camera because of scatter and diminished spatial resolution.
2. **Variations from standard protocol.** Exact imaging techniques vary among institutions. Initial thallium 201 doses range from 2 to 3.5 mCi, acquisition times vary from 20 to 40 seconds per image, and the number of images varies from 32 to 64 depending on whether 180° or 360° image acquisition is used.
 - a. The use of **360° versus 180° imaging** has been the subject of debate. With 180° tomography, contrast is better, there is less artifact, and imaging times are shorter. Slight variations also exist depending on the use of exercise stress testing or pharmacologic stress protocols.
 - b. When **exercise thallium 201 scintigraphy** is performed, the radionuclide (2 to 3.5 mCi) is usually injected approximately 1 minute before peak exercise to allow time for distribution. Initial images are obtained within 5 to 10 minutes of injection. Redistribution images are obtained 2.5 to 4 hours after the initial images.
 - c. In some cases, persistent defects that would ordinarily be interpreted as myocardial scar represent viable myocardium.
 - (1) For this reason, some advocate **delayed (late redistribution) imaging** 18 to 24 hours after injection. Some studies indicate that up to 40% of persistent defects exhibit radiotracer uptake after revascularization. Delayed imaging has resulted in further redistribution in as many as 45% of patients.
 - (2) Alternative approaches in **differentiating viable tissue from scar** include **rest reinjection** of thallium 201, in effect to boost fill-in of perfusion defects. As many as 50% of persistent defects have been shown to exhibit improved thallium 201 uptake after rest injection of 1 mCi of thallium 201, suggesting viability.
 - d. Minor changes in imaging protocol may be observed with **pharmacologic stress testing** with adenosine, regadenoson, dipyridamole, or dobutamine.
- B. **Technetium 99m.** The relative lack of redistribution requires **two injections** of technetium 99m to obtain rest and stress images.

1. Basic protocols

- a. **Same-day protocol.** At peak exercise, 25 to 30 mCi of technetium 99m is injected. Rest images are obtained first, and stress imaging follows to minimize residual scintigraphic activity caused by the higher dose stress injection.

- (1) **Rest images** are obtained with injection of 7 to 10 mCi of technetium 99m and image acquisition up to 1 to 1.5 hours later. Imaging is delayed because of slower liver clearance with rest injection.
- (2) **Stress images** are obtained approximately 45 to 60 minutes after injection. Hepatic uptake of technetium 99m occurs within 15 to 30 minutes of injection, and the tracer is excreted into the gastrointestinal tract through the biliary system. Appearance of the tracer in the gastrointestinal tract can interfere with imaging of the inferior wall of the left ventricle.
- b. The **separate-day protocol** allows time for decay of activity. Larger doses of technetium 99m can be administered for rest and stress images, and there is minimal interference between the images.
 - (1) Between 22 and 30 mCi of technetium 99m is injected for stress and rest imaging, separated by 1 to 2 days.
 - (2) The higher doses possible with the 2-day protocol produce increased count density and better image quality at the cost of inconvenience.
2. **Factors that affect image quality.** Consumption of a **fatty meal** can enhance biliary excretion of technetium 99m and improve image quality. Because of possible interference from noncardiac uptake, image processing with technetium 99m relies on normalization to the brightest cardiac pixel.
- C. **Dual isotope imaging.** Use of both thallium 201 and technetium 99m substantially reduces the time required to obtain stress and rest images.
 1. The patient receives thallium 201 at rest (3.5 mCi) and, immediately after rest imaging, undergoes stress. At peak stress, the patient is given an injection of 25 mCi of technetium 99m. Stress images are obtained 15 minutes later.
 2. This technique makes use of the dissimilar energy levels of the two radionuclides to shorten the protocol while still allowing acquisition of ECG-gated images (because of the use of technetium 99m).
 3. The sensitivity (91%) and specificity (75%) of this combination protocol are comparable to the values for conventional technetium 99m SPECT.

VII. STRESS PROTOCOLS

- A. **Exercise stress testing.** Standard exercise testing (see Chapter 49) is frequently complemented with nuclear imaging. The radioisotope is injected at peak exercise, and time is allowed for circulation of the agents (usually at least 1 minute before termination of exercise).
- B. For patients who are unable to exercise, **pharmacologic testing** is used in concert with nuclear imaging. Adenosine, regadenoson, and dipyridamole are vasodilators that are useful in noninvasive testing because of differences in coronary flow reserve. In the presence of marked coronary stenosis, the distal vessel is maximally dilated and therefore possesses little flow reserve.
 1. **Adenosine** acts at several different receptors (A_1 , A_{2A} , A_{2B} , and A_3) and thus has several physiologic effects. Its desired effect for the purpose of pharmacologic stress is to substantially enhance coronary flow in normal beds (i.e., normal flow reserve), although much less so in distributions supplied by a stenotic artery. The resultant disproportionate flow is the basis for heterogeneous radiotracer uptake.
 - a. **Administration.** Adenosine is infused at 140 $\mu\text{g}/\text{kg}/\text{min}$ for 6 minutes. The radiotracer is injected after 3 minutes of infusion.
 - b. **Side effects** commonly experienced include chest pain, headache, nausea, and flushing. Atrioventricular block and bronchoconstriction are the result of effects on the A_1 and A_3 receptors, respectively.
 2. **Dipyridamole** is an adenosine reuptake inhibitor, leading to increased extracellular concentrations of adenosine, and thus has very similar effects. It has a longer distribution half-life than adenosine, however, of approximately 25 minutes.

- a. **Administration.** Dipyridamole is infused over a 4-minute period (0.142 mg/kg/min). The maximum vasodilatory effect is achieved 4 minutes after completion of the infusion, and the radiotracer is injected at this point. A slight increase in heart rate (10 beats/min) and decrease in blood pressure (10 mm Hg) are frequently observed.
- b. **Side effects.** Headache, nausea, chest pain, hypotension, dizziness, and flushing have been reported. Severe side effects may necessitate reversal of the dipyridamole effect with aminophylline, given as a 50- to 100-mg intravenous bolus.
3. **Regadenoson** is a selective A_{2A} receptor agonist that has been FDA approved for clinical use in myocardial perfusion imaging since 2008. Two randomized double-blind multicenter trials—ADVANCE-MPI 1 and 2—have demonstrated the safety of this agent in a total of 1,871 patients, as well as an efficacy similar to adenosine for the detection of reversible perfusion defects on SPECT imaging.
 - a. **Administration.** Regadenoson is given as a single 0.4 mg (in 5 mL) intravenous bolus and does not require adjustment for body mass index or renal or hepatic function. Its coronary hyperemic effects have an onset within 30 seconds and usually last for 2 to 5 minutes.
 - b. **Side effects** of chest pain, headache, nausea, and flushing do occur with regadenoson. However, atrioventricular block and bronchoconstriction are far less common than with adenosine or dipyridamole, due to the lack of agonism of the A_1 and A_3 receptors with this A_{2A} -selective agent. Aminophylline can be given intravenously to reverse intolerable or dangerous side effects if they occur.
4. **Dobutamine** is an agonist of the β_1 and β_2 receptors and thus increases both heart rate and contractility (with a mild reduction in systemic vascular resistance).
 - a. **Administration.** Infusion is begun at 5 $\mu\text{g/kg/min}$ and increased every 3 minutes to a maximum dose of 40 $\mu\text{g/kg/min}$. The radiotracer is injected at maximum dose (or at 85% of age-predicted maximum heart rate), and the infusion is continued for 2 to 3 minutes.
 - b. **Side effects** associated with dobutamine include ectopy, headache, flushing, dyspnea, paresthesias, and hypotension.

VIII. IMAGE INTERPRETATION

- A. **Standard view of normal anatomy.** The uptake of radiotracer is homogeneous in persons with normal myocardial perfusion. The tracer is predominantly distributed to the left ventricle; the right ventricle usually appears as a faint, thin structure. Understanding and interpreting these images, however, requires an understanding of standard planar and SPECT views of LV anatomic features.
 1. **Planar images** are represented as LAO, anterior–posterior (AP), and LLAT views.
 2. Standard **SPECT views** include the short axis, vertical long axis, and horizontal long axis. The short-axis view is further divided into apical, midventricular, and basal views.
 - a. As with planar views, SPECT images in various projections **correspond with specific myocardial segments** (Fig. 48.2).
 - b. In addition to the standard SPECT sections, short-axis sections can be compiled into a so-called **bull's eye display** (i.e., **polar map**). This computer-generated polar map (i.e., “bull's eye” image) arranges short-axis tomographic images such that the central portion represents apical slices and the periphery consists of the basal segments.
- B. **Reviewing sequence.** Review of nuclear images follows an organized sequence.
 1. **Examine unprocessed images** for artifact, extracardiac uptake, and evidence of increased lung uptake.
 2. **Compare rest and stress images** for enlargement of the LV cavity.

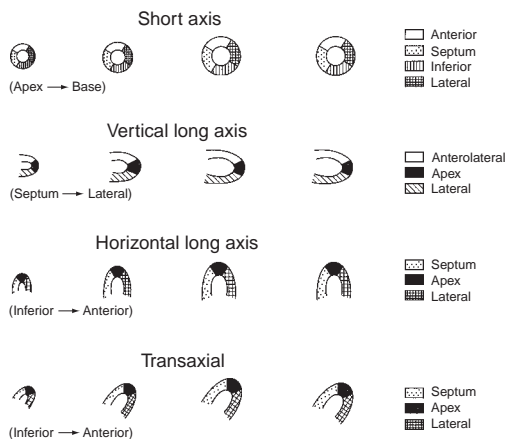


FIGURE 48.2 Standard tomographic projections and myocardial segments.

3. **Examine rest images.** Document fixed defects and the number of segments involved.
4. **Examine stress images.** Document defects and segments.
5. **Evaluate the polar map** in comparison with pooled normal images (derived from a database of patients with low probability of having CAD).
6. **Incorporate the gated SPECT images** to establish overall ventricular function and evaluate wall function in areas of questionable artifact. Segmental defects that demonstrate normal motion on gated SPECT images likely represent artifact.
- C. **Characterization of defects.** Given that initial perfusion images represent regional myocardial blood flow, defects in these images represent an area of myocardium with relatively less uptake and diminished regional blood flow. Defects can be characterized as **fixed, reversible, or partially reversible** or as displaying **reverse redistribution**. (The term *redistribution* is not appropriately used in context with technetium 99m imaging.)
 1. **Fixed defects.** Nonreversible or fixed defects are areas of absent tracer uptake that appear unchanged on both rest and stress images. Fixed defects can **represent scar or viable myocardium**. With thallium 201 imaging, nonreversibility suggests similar rates of clearance from the two regions.
 - a. **Differentiating scar from viable myocardium** in the setting of a nonreversible defect can be accomplished through the use of **metabolic radiopharmaceuticals and PET, delayed imaging, or rest reinjection** with thallium 201. The level of tracer activity reflects viability. Severe deficits (<50% of normal counts) are less predictive of viability than are milder count deficits.
 - b. Differentiating viable myocardium from scar is paramount because there is clinical and experimental evidence of improved LV function after revascularization of such hibernating regions (See Chapter 50). As methods of revascularization become increasingly applicable in an arena of increasingly complex patient problems, fully defining the so-called fixed defect through metabolic imaging assumes greater importance (see Sections **VIII.D.2** and **X.D**).
 2. **Reversible defects** are present on initial stress images but resolve on rest or delayed images. This pattern is consistent with the presence of **ischemic myocardium** in the region of reversibility.

- a. In the setting of **thallium 201 imaging**, resolution of the defect is a function of variable tracer concentrations in ischemic and nonischemic segments, which approach one another as redistribution occurs, along with continuous exchange of myocyte and blood pool thallium 201. **Fill-in** of reversible defects on thallium 201 images can be enhanced by means of delayed imaging or rest reinjection.
 - b. **Technetium 99m imaging**, which lacks redistribution, demonstrates reversibility on the basis of differential uptake during stress compared with rest.
 3. **Partially reversible defects** are present on stress images and partially resolve on rest images but do not fill in completely. This type of defect is thought to reflect a **mixture of scar and ischemic myocardium**. Nonetheless, reversibility may be incomplete even in the absence of nonviable tissue and represent purely ischemic myocardium.
 4. A pattern of **reverse redistribution** occurs when a defect appears larger on rest images or is absent on stress images but is present on rest images.
 - a. Such a pattern is seen in the presence of **acute MI** when the infarct artery has been rendered patent through thrombolysis, percutaneous coronary intervention, autolysis, or another form of revascularization.
 - b. The pattern is thought to reflect post-MI hyperemia with excess radiotracer uptake in a region of reperfused myocardium followed by accelerated myocardial washout of radiotracer in the defect region.
 - c. The regions in question may demonstrate viability on PET imaging and do not indicate ischemia.
 5. **Artifacts**. Apparent perfusion defects can be attributed to soft tissue attenuation, a problem that occurs more often with thallium 201 imaging than when a higher-energy agent (technetium 99m) is used.
 - a. Common causes of the presence of artifacts include **breast attenuation** (affecting the anterolateral, septal, anteroseptal, and posterolateral walls of the ventricle) and **diaphragmatic attenuation** (predominantly altering the inferior and posterior walls).
 - b. Planar images with perfusion defects seen in only a single view are suspect, and the presence of artifact must be considered.
 - c. SPECT artifacts may be more elusive because of processing and reconstruction of tomographic images. However, with good technique, most are avoidable. When there is a suspicion for attenuation artifacts as above, **attenuation correction** processing techniques can be employed to account for these variables.
 6. **High-risk perfusion scan**. Specific patterns of perfusion imaging that suggest high-risk coronary anatomic features include perfusion **defects in more than one vascular distribution, increased lung thallium uptake, and transient LV dilatation**.
- D. Quantitative analysis.** The principles of image analysis rely on visual inspection, which is fraught with observer variability.
1. **Computer-aided analysis** of planar data involves comparison of regional radionuclide activity on stress and rest images; count discordance coincides with reversibility. **SPECT** data are quantitatively analyzed by means of comparing count densities on short-axis images (displayed as a polar map) with normal count profiles. Although they improve sensitivity, these methods are **used in concert with visual analysis**.
 2. **PET imaging**, although evaluated in large part in a visual manner, also possesses great clinical utility with the application of **quantitative analysis of myocardial perfusion and coronary flow reserve**. Moreover, significant advances have been made in the ability to quantify *absolute*—and not just relative—blood flow in different coronary vascular territories using PET imaging. On the basis of analysis of baseline blood flow and flow during vasodilator stress, this technique is

useful in revealing functionally important coronary lesions even in the presence of multivessel coronary disease.

The administration of adenosine, dipyridamole, or regadenoson should induce at least a twofold to threefold increase in coronary blood flow over baseline in a normal coronary vascular bed—but this “flow reserve” is not present in the setting of functionally significant epicardial coronary artery stenosis existing proximally to this bed (as discussed earlier in the chapter). Thus, relative differences in myocardial perfusion during hyperemia—which may not be appreciated on visual inspection—may be more precisely demonstrated with quantitative analysis of flow reserve. Furthermore, the ability to quantitate absolute myocardial blood flow regionally and globally may help surmount the difficulty in noninvasively diagnosing CAD in the setting of “balanced ischemia” from severe left-main or triple-vessel CAD.

IX. CLINICAL APPLICATIONS

A. Perfusion analysis

1. Detection of CAD

a. **Sensitivity and specificity.** Since the introduction of thallium 201 imaging in 1975, the utility of perfusion agents in the diagnosis of CAD has been well established. Quantitative planar imaging and SPECT demonstrate 90% or greater sensitivity.

(1) **Sensitivity** is affected by the number of vessels involved. Single-vessel disease is most likely to produce a false-negative finding. Multivessel CAD rarely produces a normal perfusion scan result. The **specificity** of planar imaging is 83% and that of SPECT is ~70%.

(2) In general, radionuclide imaging is best used to evaluate a population at intermediate risk for CAD. The choice of radionuclide agent seemingly has little effect on the accuracy of these techniques.

(3) The introduction of **PET**, however, has brought with it **advanced diagnostic accuracy**, with approximately 10% to 15% improvement over SPECT. The ability to detect CAD in a noninvasive manner offers numerous additional applications in risk stratification, prognosis, and imaging of acute infarction.

b. Causes of **false-positive** perfusion study results include attenuation defect, technical inadequacies, coronary vasospasm, anomalous coronary circulation, cardiomyopathy, conduction defects such as left bundle branch block, and recanalization of a thrombosed coronary artery.

c. Causes of **false-negative** perfusion study results include a submaximal exercise stress test, anti-ischemic medical therapy, collateral or overlap circulation, inaccurate interpretation of perfusion images or angiograms, acquisition of suboptimal images, presence of balanced coronary stenoses, and delay in stress imaging.

2. **Risk stratification.** In addition to indicators of higher risk taken from perfusion images, such as increased lung uptake, determinants in the assessment of risk are as follows.

a. **Presence of reversible as opposed to fixed defects** is associated with greater likelihood of cardiac events related to acute coronary syndrome at follow-up evaluation. This relation has clinical utility in a number of settings, including risk stratification after MI or in the preoperative setting. In one study involving patients who had had MI without complications, patients with single, fixed defects on thallium 201 images had a 6% cardiac event rate, compared with a rate of 51% for those with thallium 201 scans that indicated high risk of such an event.

b. Radionuclide **imaging abnormalities** have been identified as **independent predictors of subsequent infarction or death**. In general, the number of

abnormal segments identified on nuclear images can be seen as inversely proportional to survival rate. Normal findings on a nuclear perfusion study, however, suggest an excellent prognosis, with a yearly mortality rate <1% (in patients with a normal ejection fraction). The application of such prognostic information to the care of patients preparing for noncardiac operations reflects significantly on the patient's surgical risk and has an established role in preoperative evaluation and clearance. For this population, evidence of ischemia on perfusion images portends a higher risk of a perioperative cardiac event.

3. Myocardial perfusion imaging may aid in the diagnosis and risk stratification of patients with **acute coronary syndromes**.
 - a. Patients with **chest pain of ill-defined origin** can be given an injection at rest of thallium 201 or technetium 99m. In the presence of true ischemia (i.e., without infarction), **reversible defects** are documented, and insight into **regional distribution of ischemia** and extent of myocardium involved is gained. The **absence of any perfusion defect with ongoing chest pain makes a diagnosis of angina less likely**.
 - b. In the setting of **thrombolysis**, imaging with technetium 99m can provide important information about reperfusion or lack thereof. Injection of technetium 99m before initiation of thrombolysis captures a picture of hypoperfusion, which can, because of the extensive half-life, be imaged at a later time. Subsequent injections reveal the status of perfusion as the period after thrombolysis proceeds (i.e., persistent, large defect that represents failed reperfusion). Such applications in the setting of thrombolysis and in acute coronary syndromes have limited clinical utility because of the logistics of staffing and availability of radiopharmaceuticals.
 - c. A further application that affects the arena of revascularization and management of ischemic syndromes involves **assessment of myocardial viability**.
- B. **Assessment of ventricular function.** In addition to its use in perfusion analysis, radionuclide imaging can establish cardiac performance. Radionuclide-based assessment of ventricular function includes first-pass radionuclide angiocardiology and gated blood pool imaging.
 1. **First-pass radionuclide angiocardiology** involves injection of a radionuclide and analysis as the agent passes through the central circulation.
 - a. Technetium 99m-labeled agents are typically administered in bolus form, and scintigraphic data are recorded for 15 to 30 seconds after injection. Multicrystal cameras oriented in a straight anterior projection are used for detection of high count rates.
 - b. This method of ventricular function analysis is more useful in evaluating **right ventricular function** than is gated blood imaging. In patients with **severe LV dysfunction**, the radiotracer may be dispersed, and proximal venous access and rapid administration may be necessary.
 2. **Gated blood pool imaging**, also known as radionuclide angiography or MUGA, relies on ECG gating to correlate multiple individual images of the cardiac blood pool to specific phases of the cardiac cycle.
 - a. The blood pool is labeled by means of removing a 2- to 3-mL sample of the patient's blood after the intravenous administration of stannous chloride. The sample is labeled with technetium 99m and reinjected into the patient intravenously. The stannous ions reduce the technetium, so they will not leak out of the tagged cells.
 - b. A single-crystal gamma camera is used in the LAO, AP, LLAT, and sometimes left posterior oblique projections to obtain serial static images of the cardiac blood pool gated to the R-R interval.
 - c. Because multiple cardiac cycles are averaged to obtain the final images, this technique is not optimal for evaluating regional wall motion. For many years, though, MUGA was considered a "gold standard" technique

for assessment of overall LV ejection fraction. Radionuclide angiography remains a well-validated and highly reproducible method of assessment of overall LV ejection fraction (and, importantly, retains this quality especially well at low ejection fractions). The use of this technique is diminishing in the current era of echocardiography and cardiac MRI.

3. **ECG-gated perfusion imaging.** Perfusion imaging with technetium 99m-labeled tracers produces sufficient count densities on individual images to allow ECG gating. The standard injection of 20 to 30 mCi of technetium 99m allows evaluation of **perfusion and function in a single study**. The *greatest* utility of ECG-gated perfusion imaging may be in elucidating perceived artifacts on perfusion images. For example, if a region has a perceived fixed perfusion defect, yet wall motion is normal in the same region, artifact becomes a more likely consideration as the cause of the filling defect.

Comparison of this method with two-dimensional echocardiography in the evaluation of regional wall motion has shown good correlation between the two. This correlation is not applicable to stress echocardiography, however, because of the time lag from the period of stress to the acquisition of nuclear images.

- X. **POSITRON EMISSION TOMOGRAPHY.** PET has bolstered the evaluation of CAD by nuclear imaging techniques, both by improving blood flow imaging and by allowing evaluation of metabolic activity. Positron imaging agents can be divided into blood flow tracers and metabolic radiopharmaceuticals.

- A. **Blood flow tracers.** A number of radiopharmaceuticals exist for the assessment of myocardial blood flow. They can be produced by a cyclotron or generator.

1. **Rubidium 82**, the most readily used blood flow tracer, can be generated on-site without the use of a cyclotron. Much like thallium 201, rubidium 82 is a potassium analogue that is actively transported into myocytes through the Na-K pump. **Uptake into myocardium** is proportionate to regional blood flow. Approximately 65% of the radiotracer is extracted at first pass. Because of a short half-life (76 seconds), rubidium 82–based imaging protocols can be used to assess myocardial blood flow rapidly (within 1 hour). However, the short half-life also precludes exercise stress PET imaging with this tracer.

2. Other perfusion agents include the cyclotron-produced **nitrogen 13 ammonia** (half-life 10 minutes) and **oxygen 15 water** (half-life 123 seconds). Image quality with **oxygen 15 water** is poor and requires extensive processing to subtract the blood pool. Rb 82 and ¹³N-ammonia are the perfusion tracers that are used in clinical practice, with Rb 82 carrying the distinct advantage of requiring only a generator instead of a cyclotron. The image quality of ¹³N-ammonia is excellent, although the impracticality of cyclotron production in most facilities is a limiting factor for this agent. For those facilities capable of ¹³N-ammonia generation, however, it has the “upside” of a longer half-life than rubidium 82; thus, exercise stress cardiac PET imaging could be performed if desired.

- B. **Metabolic radiopharmaceuticals.** Metabolic imaging with PET depends on the use of radiolabeled substrates of cardiac metabolism, largely in the form of [¹⁸F] fluoro-2-deoxyglucose (FDG), carbon 11 palmitate, and carbon 11 acetate.

1. **FDG** is a glucose analogue used by ischemic myocardium because of a transition to alternative fuel sources in the hypoxic state. Ischemic myocardium diminishes the oxidation of long-chain fatty acids and increases the use of glucose as a secondary fuel source. FDG is phosphorylated to FDG-6-phosphate after transport across the cell membrane. FDG imaging therefore reflects myocardial use of exogenous glucose, and FDG is a widely used metabolic radiopharmaceutical. It has a half-life of 1.83 hours, which means it can be ordered on a daily basis by institutions that do not have an on-site cyclotron—making it the most commonly used metabolic PET imaging agent.

2. [^{11}C]Palmitate is taken up by myocytes, converted to acyl CoA, and relegated to triglyceride stores or β -oxidized to produce [^{11}C]carbon dioxide. The release of this product of β -oxidation is reflective of long-chain fatty acid oxidation in myocardium.
 3. [^{11}C]Acetate is metabolized to [^{11}C]carbon dioxide after entering the tricarboxylic acid cycle. Measuring the production of [^{11}C]carbon dioxide in this setting correlates with myocardial oxygen consumption.
- C. Protocols.** Image acquisition with PET is similar to that with SPECT in that tomographic images are obtained in short-axis, horizontal long-axis (sagittal), and vertical long-axis (coronal) views. A positron camera consists of an array of crystals arranged in a circle. Unlike in SPECT, the camera remains stationary in PET.
1. The heart is localized with the patient's arms extended above the head. An **attenuation scan** is performed that allows the density of the surrounding thorax to be subtracted to leave only cardiac count activity. This performance of attenuation correction which makes **allowance for noncardiac interference** adds a great deal to the accuracy of PET.
 2. After the attenuation scan, the **positron-emitting radiopharmaceutical is injected, and images are obtained** 2 to 5 minutes later. As mentioned earlier in the chapter, two photons are created by the annihilation of the emitted positron colliding with the nearest electron it meets in the tissue surrounding it. These two photons travel *exactly 180° apart* while the patient is lying in the circular scanner. This is an important concept because it means there is **no need for collimation**. The detector/analyzer merely has to "accept" the signal it receives only if a simultaneous signal strikes the detector directly across from it in the scanner. This *dramatically* improves the signal-to-noise ratio that can be achieved during imaging.
 3. Metabolic imaging can be undertaken after flow imaging with the administration of 5 to 10 mCi of FDG. Tomographic images are typically obtained 30 to 50 minutes after FDG injection.
- D. Patterns of perfusion and metabolic imaging.** Specific patterns of perfusion and metabolic imaging are identifiable. For example, **normal flow–normal FDG (match)** indicates normal perfusion and normal metabolic activity. **Reduced flow with normal or increased FDG ("flow-metabolism mismatch")** demonstrates viability (i.e., hibernating myocardium). **Reduced flow–reduced FDG** identifies scar tissue.
- E. Clinical applications**
1. **Diagnosis of CAD.** Flow imaging with PET is highly sensitive and highly specific for the detection of coronary stenosis, approaching 93% for both.
 - a. Higher-energy photons (511 keV), higher count densities, shorter half-life, and "built-in" attenuation correction place PET substantially ahead of SPECT in the accurate detection of CAD.
 - b. As mentioned before, the ability to quantitate absolute blood flow regionally and globally may help improve the diagnosis of coronary ischemia in the setting of severe multivessel disease and balanced ischemia.
 2. **Assessment of myocardial viability.** (see Chapter 50). The use of **PET with metabolic radiotracers is the standard for identifying viable myocardium**. The presence of a flow-metabolism mismatch, which indicates underperfusion in the presence of metabolically active myocytes, indicates hibernating myocardium. Revascularization of these zones as identified with PET has been shown to result in improvement in wall motion. This utility of nuclear imaging has found increasing application in the selection of patients for revascularization who have ischemic cardiomyopathy and heart failure with low ejection fraction.

ACKNOWLEDGMENTS: *The author would like to thank Drs. Jeffrey A. Skiles and Gregory Bashian for their contributions to earlier editions of this chapter.*

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CHAPTER

49

Michael P. Brunner

Stress Echocardiography

- I. **INTRODUCTION.** Stress echocardiography (SE) is an **effective method of evaluating for myocardial ischemia**, based on the detection of **stress-induced regional wall motion abnormalities** (WMAs). Stressors include exercise, pharmacologic agents, and pacing. SE is used to **screen for coronary artery disease** (CAD), and it can help **identify the coronary vessels involved**. The accuracy of SE in the detection of significant coronary artery stenosis is 80% to 90%, which is superior to that of exercise electrocardiographic testing and comparable to that of nuclear stress imaging. In patients with left ventricular (LV) dysfunction and documented CAD, SE can **differentiate viable myocardium from scarred myocardium**, which may help predict whether LV function will improve after revascularization. As a diagnostic test for CAD, **SE is safe and relatively inexpensive** and **can be rapidly performed by experienced hands**. However, interpretation of SE images remains primarily subjective and requires a considerable learning curve. SE can also be used to assess the severity of valvular disease, hypertrophic cardiomyopathy, and exercise-induced pulmonary hypertension. In addition, it provides important prognostic information after myocardial infarction (MI) and prior to noncardiac surgery.

II. PATHOPHYSIOLOGY

- A. Exercise stress testing.** Myocardial ischemia results from a mismatch between oxygen supply and demand. The ischemic cascade is illustrated in Figure 49.1. Echocardiography detects ischemia by identifying new or worsening WMAs earlier in the cascade than detected by the electrocardiogram (ECG) or the onset of symptoms, but usually after the onset of worsening diastolic function. Exercise can be performed with a treadmill or an upright or supine bicycle.
- B. Pharmacologic stress testing.** In patients who cannot exercise, pharmacologic stressors can be used. These drugs are sympathomimetic agents or vasodilators.
- 1. Sympathomimetic agents.** Myocardial oxygen demand is determined by contractility (inotropy), heart rate (chronotropy), and wall stress (preload + afterload). Sympathomimetic agents produce stress by causing an **increase in myocardial oxygen demand through increased inotropy, chronotropy, and blood pressure (BP) (afterload)**. Although a number of agents have been evaluated in combination with echocardiography, **dobutamine** is most widely used. Low-dose dobutamine has positive inotropic effects mediated through cardiac α_1 and β_1 receptors. At higher doses, it has positive chronotropic effects mediated through β_2 receptors. The plasma half-life of dobutamine is 2 to 3 minutes. The normal response to dobutamine is an increase in heart rate and hyperdynamic wall motion, with only minimal effect on end-diastolic LV volume. It can be **combined with atropine** to achieve the usual target of at least 85% of age-predicted maximum heart rate (APMHR).
 - 2. A vasodilator stress test** is performed with **dipyridamole** or **adenosine** infusion. These agents result in perfusion abnormalities by causing blood to be preferentially shunted away from myocardial segments supplied by stenotic coronary arteries (i.e., coronary steal) and into more normal coronary vessels. This may lead to wall motion abnormality in the perfusion territory of the stenotic coronary artery that is seen on echocardiography. These agents are less commonly used for SE. Adenosine has fewer side effects than dipyridamole, owing to the former's shorter half-life. However, because of the shorter duration of action of adenosine, the echocardiographic findings tend to be less pronounced and of shorter duration, resulting in a lower sensitivity.

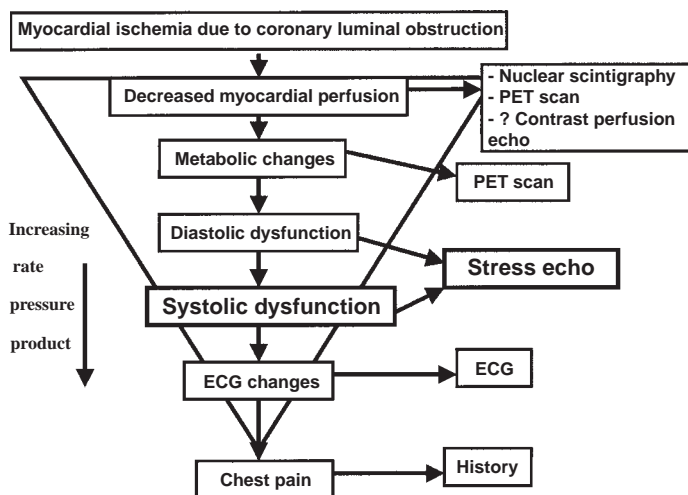


FIGURE 49.1 Ischemic cascade. PET, positron emission tomography; ECG, electrocardiogram.

3. **The 2007 American Society of Echocardiography (ASE) guidelines recommend dobutamine as the first-line agent for pharmacologic SE.** In addition, much of data for preoperative risk stratification and viability assessment using SE were derived from pharmacologic studies using dobutamine.
- C. **Atrial pacing.** Tachycardia induced by atrial pacing is an alternative to pharmacologic testing in patients that cannot exercise. In patients with a permanent pacemaker, stress is achieved by increasing the pacing rate until the target heart rate is reached. Transvenous and transesophageal pacing are considerations in patients without a permanent pacemaker.

III. INDICATIONS AND CHOICE OF STRESSOR

- A. The **indications and contraindications** for SE testing are similar to those used for exercise electrocardiographic stress testing (see Chapter 47). The addition of an imaging modality improves the sensitivity and specificity of exercise electrocardiographic stress testing. Table 49.1 lists factors that may limit the sensitivity of electrocardiographic stress testing to detect CAD; patients with these factors benefit from a stress test utilizing an imaging modality (i.e., echocardiography, nuclear scintigraphy, or positron emission tomography [PET]).
- B. **Additional contraindications** to SE occur **with pharmacologic stress** and depend on the underlying pharmacologic stressor. Patients with severe bronchospastic obstructive lung disease or high-grade atrioventricular (AV) block should avoid dipyridamole and adenosine. Patients with unstable ventricular arrhythmias should avoid dobutamine infusion. **Relative contraindications to SE** include unstable angina, severe baseline hypertension, uncontrolled arrhythmias, mobile LV thrombus, critical aortic stenosis (AS), hypertrophic obstructive cardiomyopathy, and decompensated heart failure.
- C. Exercise stress is preferred over nonexercise stress because it more closely reproduces daily activity and is more sensitive in the detection of ischemia, provided the patient is able to achieve an adequate level of stress. No single **exercise modality** has been shown to have superior sensitivity, although the **treadmill** is more widely accepted among patients and physicians. **Bicycle ergometry** can be performed in the upright and supine positions. Images with treadmill stress testing must be obtained after exercise, whereas images may be obtained at peak exercise with bicycle ergometry while the patient continues to exercise. The sensitivity of treadmill testing to detect ischemia is reduced if images are not rapidly obtained (< 90 seconds) after exercise. However, the treadmill usually results in a greater level of stress than is associated with bicycle ergometry, which is more dependent on patient effort.

TABLE 49.1 Factors Limiting the Sensitivity of Stress Electrocardiography to Detect Coronary Artery Disease

Left bundle branch block or other intraventricular conduction delay abnormalities
Paced rhythms
Abnormal ST segments at baseline:
Digitalis effect
Electrical left ventricular hypertrophy
Previous evidence of myocardial infarction
Nonspecific, abnormal ST-segment changes
Women (higher rate of false-positive ST-segment changes)
Left ventricular hypertrophy (even with normal-appearing electrocardiogram)

- D. Up to 30% of patients referred for exercise echocardiography may not be able to achieve an adequate level of exercise stress because of peripheral vascular disease, chronic obstructive pulmonary disease, or musculoskeletal problems. Pharmacologic stress testing is usually indicated in these patients.

IV. METHODOLOGY

A. Patient preparation

1. Patients should avoid heavy food intake for several hours before the test.
2. Rate-slowing agents (particularly β -blockers) blunt the normal heart rate response to exercise and may limit the ability of the patient to achieve at least 85% of the APMHR. This may reduce the sensitivity of the test results. If possible, these agents should be withheld before the stress test, unless the aim of the test is to evaluate their effectiveness in preventing exercise-induced ischemia.
3. The standard connections for a 12-lead ECG may be used with minor modifications to allow imaging in the parasternal and apical windows without affecting the accuracy of the exercise electrocardiographic testing results.

- B. **Equipment.** All SE studies are conducted with exercise electrocardiographic testing and standard hemodynamic monitoring equipment. A SE software package on the echocardiographic machine is necessary to acquire digital images and to allow side-by-side comparison of pre-stress images with peak stress or post-peak stress images. Resuscitation equipment and a defibrillator should be readily available.

C. Performing the test

1. **Exercise SE.** Regardless of the exercise modality, a quick, complete baseline echocardiographic scan is obtained for all patients. Resting images are obtained in the parasternal long- and short-axis and apical two- and four-chamber views and stored digitally. An apical long-axis view may be substituted for a parasternal long-axis view if the parasternal images are suboptimal. If endocardial definition is suboptimal, intravenous ultrasound contrast should be given to optimize the images.
 - a. **Treadmill exercise** is performed with standard protocols according to the functional status of the patient. Exercise is continued until at least 85% of the APMHR is reached, but it is preferably continued to the level of maximum exertion to maximize test sensitivity. APMHR equals $220 - \text{age}$. Post-peak stress images are obtained as quickly as possible (in the left lateral decubitus position) after the patient transfers from the treadmill to the imaging table. Stress images in the same views as the baseline study are stored digitally and recorded on videotape. All post-peak stress images should be obtained within 90 seconds of completing exercise to maximize test sensitivity.
 - b. During upright bicycle echocardiography, baseline images are obtained in the standard left lateral position and are repeated with the patient in the upright position on the cycle ergometer. Adequate parasternal images may be recorded by having the patient lean forward. These images are recorded and digitized to allow comparable windows for the rest and peak stress images. Cycle ergometry is started at a workload of 25 W and increased by 25 to 50 W every 2 to 3 minutes until the patient reaches his or her level of perceived maximal effort. During upright bicycle echocardiography, images are obtained and digitized at rest, before peak, at peak, and after peak exercise.
 - c. With supine bicycle exercise, the entire study is performed while the patient is tilted 30° in the left lateral decubitus position, and images are obtained and digitized at rest, before peak, at peak, and after exercise. This exercise modality is not widely used.
 - d. **Study end points** for exercise SE include target heart rate (85% APMHR), severe electrocardiographic ischemia (ST-segment depression > 5 mm), intolerable symptoms (chest pain and dyspnea), severe hypertension

(systolic BP > 220 mm Hg or diastolic BP > 110 mm Hg), **hypotension** (systolic BP < 90 mm Hg or a fall in systolic BP > 20 mm Hg from baseline), **ventricular tachycardia** or **sustained supraventricular tachycardia**, and the **development of new WMAs in at least two contiguous segments**.

2. Pharmacologic SE

a. Dobutamine SE

- (1) **Dobutamine infusion** is started at 10 $\mu\text{g/kg/min}$ and increased every 3 minutes to 20, 30, and 40 $\mu\text{g/kg/min}$. If the patient has not reached 85% of APMHR by the end of the 40 $\mu\text{g/kg/min}$ dose, a 3-minute dosage of 50 $\mu\text{g/kg/min}$ may be used. Infusion is begun at lower doses (5 $\mu\text{g/kg/min}$) if baseline LV function is abnormal and myocardial viability is being sought. Images are digitized at rest and at low dosage (5 to 10 $\mu\text{g/kg/min}$), pre-peak dosage (30 $\mu\text{g/kg/min}$), and peak dosage.
- (2) **Atropine** is used as needed to reach target heart rate > 85% of APMHR if dobutamine alone is not effective. Atropine (0.25 to 0.5 mg) is given intravenously every minute, starting at the 40 $\mu\text{g/kg/min}$ dobutamine dose level and continuing until an end point is reached or a total dose of 2 mg is given. Atropine should be used with caution in patients that have glaucoma or benign prostatic hypertrophy. Isometric handgrip may be performed at the peak infusion rate to help achieve target heart rate.
- (3) **Study end points** for dobutamine SE are the same as those used for exercise SE. If 85% APMHR has been achieved without any other end points, it is preferable to complete the protocol to the end of the 40 $\mu\text{g/kg/min}$ infusion to increase the sensitivity of the test.
- (4) **Side effects.** The most serious potential side effect of dobutamine is arrhythmia provocation. However, serious complications (e.g., arrhythmia, MI, and cardiac arrest) are rare, occurring in about 0.3% of studies in a large series of > 5,000 patients. Less serious side effects include tremor, nervousness, and marked hypertensive and hypotensive responses. The most common minor complication is hypotension, which usually responds to supportive therapy including intravenous fluids. A hypotensive response with dobutamine may be caused by ischemia and dynamic outflow tract obstruction or may result from the vasodilatory effect of dobutamine in combination with a small hyperdynamic LV and a low stroke volume.
- (5) **If angina or severe side effects develop,** the effects of dobutamine may be **reversed with intravenous β -blockade** (0.5 to 1 mg/kg esmolol given over 1 minute or 2 to 5 mg/kg metoprolol given every 2 to 5 minutes). Like dobutamine, esmolol has a very short half-life and, therefore, may be preferable.

b. Dipyridamole or adenosine SE

- (1) Patients with hypotension, AV block, or a history of severe bronchospasm **should not undergo** testing with these agents.
- (2) Different protocols of **dipyridamole infusion** have been studied. The protocol recommended by the ASE is a low-dose two-stage infusion. The first stage begins at 0.56 mg/kg dipyridamole over 4 minutes; if no adverse effect or clinical end points are reached, an additional 0.28 mg/kg is infused over 2 minutes. **A high-dose** regimen of 0.84 mg/kg given over 10 minutes has been developed to improve the sensitivity of the test relative to low-dose protocols.
- (3) **Adenosine** is given as a continuous infusion because of its very short half-life. A typical protocol starts at a low dose of 80 $\mu\text{g/kg/min}$ and is increased every 3 minutes by 30 $\mu\text{g/kg/min}$ to a peak dose of 170 to 200 $\mu\text{g/kg/min}$.
- (4) **Regadenoson** is an adenosine receptor agonist with a 2 to 3-minute half-life, as compared with adenosine's 30-second half-life. Regadenoson is administered as one 0.4-mg dose over 10 seconds.

(5) **Study end points** for dipyridamole or adenosine SE are similar to those used for exercise SE. A notable exception is that patients are not stressed until the APMHR is achieved. Additional end points include third-degree AV block, severe hypotension, and intolerable side effects (e.g., bronchospasm). Symptoms usually start to resolve within 60 seconds after medication administration.

(6) **If hypotension, bradycardia, or bronchospasm occurs**, the effects of dipyridamole, adenosine, and regadenoson can be **reversed with intravenous aminophylline** 25 to 50 mg over 30 to 60 seconds.

D. Imaging techniques. Modern technology allows digital image acquisition of multiple cardiac cycles and side-by-side comparison in a split screen display, enabling easy comparison of regional wall motion at rest and peak stress or after stress. Detailed frame-by-frame evaluation of wall thickening or excursion is possible, which helps in the evaluation of regional myocardial function. Obesity and lung disease remain the primary reasons for poor quality images. **Harmonic imaging** has improved endocardial definition, which can be further optimized with **microbubble contrast agents**.

1. **Contrast echocardiography.** Microbubble contrast agents provide **improved echocardiographic resolution** and allow **real-time assessment of intracardiac blood flow**. These agents are helpful when baseline SE images are suboptimal.

a. **Intravenous agitated saline** improves visualization of the right atrium and ventricle and enables visualization of intracardiac shunts. However, intravenous agitated saline is not able to cross the pulmonary circulation and opacify the left ventricle.

b. **Second-generation microbubble contrast agents** such as **Optison** and **Definity** incorporate perfluoropropane gas encased in an albumin-based or phospholipid shell, are more durable, and are able to cross the pulmonary circulation and opacify the left ventricle.

c. **These agents are well tolerated and have a low complication rate.** After initial concerns about safety, the FDA revised labeling requirements for second-generation contrast agents in 2008 and again in 2011. Patients with pulmonary hypertension or unstable cardiopulmonary conditions including acute coronary syndrome, worsening or unstable heart failure, serious ventricular arrhythmias, or respiratory failure no longer need to have their vital signs and oxygen saturation monitored for 30 minutes after injection. **Absolute contraindications to administration include previous hypersensitivity reaction and fixed right-to-left, bidirectional, or transient right-to-left cardiac shunts.** Intra-arterial injection is contraindicated.

2. **Real-time three-dimensional (3D) echocardiography.** Significant advances have been made in 3D data acquisition without the need for off-line reconstruction. Three-dimensional imaging may shorten the acquisition period of post-exercise images or peak exercise images, allowing improved sensitivity and minimizing the technical strains imposed on the technologist obtaining the images. However, 3D SE is not routine in clinical use and remains under investigation.

V. IMAGE INTERPRETATION

A. Qualitative versus quantitative approach

1. **Interpretation of SE findings is predominantly qualitative.** Visual assessment of LV wall thickening and motion remains the standard method of interpretation of SE but is **subject to interobserver and interinstitutional variability**. Suggestions to optimize interpretation of SE images are outlined in Table 49.2. Each myocardial segment is visually assessed for wall thickening, rather than just wall motion, which may be influenced by myocardial tethering and translation. LV wall motion normally becomes hyperdynamic with stress. Worsening of WMAs or the development of new ones is the hallmark of stress-induced myocardial ischemia. SE responses and interpretation are summarized in Table 49.3.

TABLE 49.2 Suggestions to Optimize Interpretation of Stress Echocardiographic Images

1. Ensure that pre-stress and post-stress images are comparable views
2. Ensure that the apex is not foreshortened, especially in two-chamber views
3. True two-chamber views should not show any of the right ventricle
4. Use ultrasound microbubble contrast agents when resting images are suboptimal
5. Check that digital images are timed to begin at systole. If digital clips include diastole, there is an increased likelihood of calling a false-positive wall motion abnormality
6. Check the heart rate for each post-stress image. If images are obtained after the heart rate has returned toward normal, the sensitivity of the test will be reduced
7. Compare the wall motion of individual segments from rest to stress in the four-screen display to define ischemia and infarction. Then compare segments in the post-stress images to identify differences in contraction and in the development of “hinge points”
8. Confirm any wall motion abnormality in a second view if possible
9. Avoid overcalling ischemia in the basal inferior or basal septal segments
10. Avoid calling a new wall motion abnormality if it is limited to only one myocardial segment; the abnormality should involve at least two contiguous segments

TABLE 49.3 Stress Echocardiographic Responses and Interpretation

Resting or baseline function	Response to low-dose pharmacologic stress	Peak and post-stress function	Interpretation
Normal	Normal	Hyperdynamic	Normal myocardium
Normal	Normal or new WMA	New WMA or lack of hyperdynamic response; LV dilation or decreased EF (with exercise only)	Ischemic myocardium
WMA	No change	No change	Infarcted myocardium
WMA	Improved	Decreased (biphasic response)	Viable (hibernating) myocardium
WMA	No change	Improved	Nonspecific

WMA, wall motion abnormality; LV, left ventricular; EF, ejection fraction.

2. **Quantitative methods** of analysis improve the reproducibility of interpretation and enhance the detection of CAD, particularly by less experienced physicians. However, at this time, **the ASE recommends further validation and simplification of quantitative analysis methods before they can be recommended for routine use.** Examples of quantitative analysis methods include Doppler assessment of global systolic and diastolic function; automated endocardial border detection using integrated backscatter; and tissue Doppler assessment of myocardial displacement, velocity, strain, and strain rate.
 - a. **Tissue Doppler assessment** along the long axis using apical views allows quantification of regional longitudinal myocardial function. Tissue Doppler

is thought to be a potentially sensitive marker of subendocardial ischemia because abnormalities in regional contraction occur earlier in longitudinal than radial segments.

- b. **Strain rate** is a measure of the speed or velocity of regional myocardial contraction (time from QRS to the onset of regional myocardial relaxation). During dobutamine SE, strain rate increases (interval of time from QRS to myocardial relaxation decreases) in normal hearts and is reduced in areas of myocardial ischemia. The optimal cutoff for strain rate that gives the best sensitivity and specificity has been reported to be an increment of < 0.6 per second. Strain rate imaging is a reliable predictor of coronary stenosis, is **more specific** than visually assessed wall motion scoring, and may allow readers to detect intermediate severity coronary stenosis that produces only subtle WMAs.

B. 17-Segment model. Regional wall motion is assessed using a 17-segment model (Fig. 49.2), with results geographically represented on a circumferential polar plot (Fig. 49.3). A **16-segment model** had previously been utilized for SE, whereas a 17-segment model was utilized for other cardiovascular imaging modalities including magnetic resonance imaging, nuclear scintigraphy, and PET. In 2002, the American Heart Association (AHA) proposed that all tomographic cardiovascular studies utilize the 17-segment model to allow for standardized segmentation and nomenclature. The ASE recommended the 17-segment model in their 2007 SE guidelines.

1. The individual **myocardial segments can be assigned to coronary artery territories**, as illustrated in Figure 49.4. Of note, this approach makes assumptions that are not always correct due to anatomic variability. For instance, the left anterior descending coronary artery does not always supply the entire apex and the posterior wall is not always supplied by the left circumflex coronary artery. The system may also be problematic if multivessel disease is present, in which case the territory with the most ischemia is identified and less severe lesions may not be apparent.
2. Wall motion is **subjectively graded** as normal, mildly hypokinetic, severely hypokinetic, akinetic, or dyskinetic and may be assigned a wall motion score of 1 to 4 (normal, hypokinetic, akinetic, dyskinetic, respectively). Each myocardial segment in the rest and stress images is graded in this manner.

C. Exercise SE

1. A **normal response** to exercise stress includes a global increase in contractility, the development of hyperdynamic wall motion, and a gradual rise in the heart rate. This is manifested by increased wall thickness and increased endocardial excursion with stress.
2. **Resting WMAs** usually indicate prior MI, although regional variability may be seen in diffuse myopathic processes. Resting WMAs may be defined as hypokinetic, akinetic, or dyskinetic. Akinesia and dyskinesia usually indicate transmural infarction, whereas hypokinetic segments may be partially infarcted or viable.
3. An **abnormal response to exercise is defined by the development or worsening of regional myocardial function**. Regional myocardial dysfunction, as **manifested by decreased endocardial excursion and wall thickening**, is **specific for myocardial ischemia**. Decreased excursion alone is less specific and can occur with conduction abnormalities and paced rhythms and in the normal basal inferior myocardial segments.
4. **Adjunctive diagnostic criteria** for a positive SE examination include **LV cavity dilation, a decrease in global systolic function diastolic dysfunction, and new or worsening MR**. However, these adjunctive diagnostic criteria are **more specific for detecting severe CAD and may not be sensitive** for detecting the presence of CAD.
5. **False-positive findings** may occur with left bundle branch block (septal WMA) and right ventricular pacing (apical WMA). A hypertensive response to exercise can cause LV dilation and systolic dysfunction.

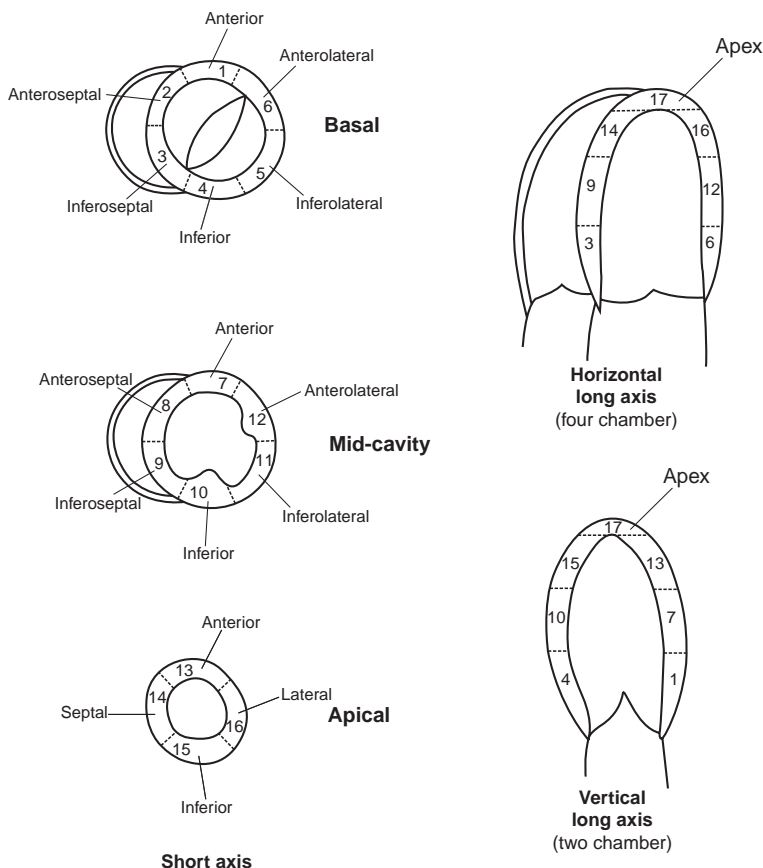
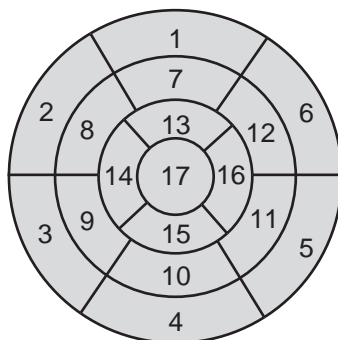


FIGURE 49.2 Diagram of vertical long-axis, horizontal long-axis, and short-axis planes showing the name, location, and anatomic landmarks for selection of the basal (tips of the mitral valve leaflets), mid-cavity (papillary muscles), and apical (beyond papillary muscles but before cavity ends) short-axis slices for the 17-segment system. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

6. **False-negative findings** may occur with delay in capturing post-exercise images or low workload or heart rate response (i.e., inadequate stress). Additional causes of false-positive and false-negative findings are outlined in Table 49.4.
- D. **Pharmacologic SE.** With only a few exceptions, the principles of interpretation of pharmacologic SE findings are similar to those used for exercise echocardiography.
 1. The **typical ischemic response to dobutamine** is characterized by normal resting wall motion and an initial **hyperdynamic response at low doses followed by a decline in function at higher doses**. Ischemia may also be identified on the basis of deterioration of normal wall motion without any transient hyperdynamic response.

Left ventricular segmentation



- | | | |
|------------------------|-----------------------|---------------------|
| 1. Basal anterior | 7. Mid-anterior | 13. Apical anterior |
| 2. Basal anteroseptal | 8. Mid-anteroseptal | 14. Apical septal |
| 3. Basal inferoseptal | 9. Mid-inferoseptal | 15. Apical inferior |
| 4. Basal inferior | 10. Mid-inferior | 16. Apical lateral |
| 5. Basal inferolateral | 11. Mid-inferolateral | 17. Apex |
| 6. Basal anterolateral | 12. Mid-anterolateral | |

FIGURE 49.3 Display, on a circumferential polar plot, of the 17 myocardial segments and the recommended nomenclature for tomographic imaging of the heart. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

Coronary artery territories

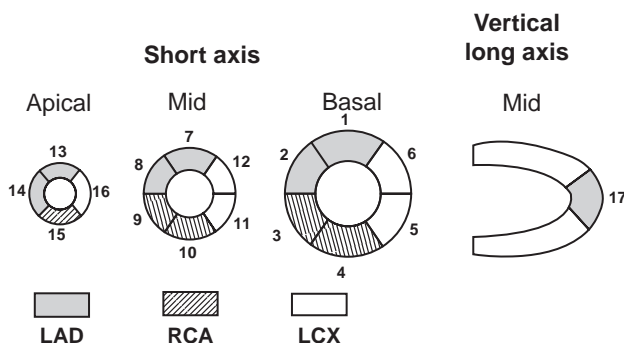


FIGURE 49.4 Assignment of the 17 myocardial segments to coronary artery territories. LAD, left anterior descending; RCA, right coronary artery; LCX, left circumflex coronary artery. Reproduced with permission from Cerqueira MD, Weissman NJ, Dilsizian V, et al. Standardized myocardial segmentation and nomenclature for tomographic imaging of the heart: a statement for healthcare professionals from the Cardiac Imaging Committee of the Council on Clinical Cardiology of the American Heart Association. *Circulation*. 2002;105:539–542.

TABLE 49.4 False-Positive and False-Negative Stress Echocardiographic Test Results

Causes of incorrect stress echocardiographic interpretation	Factors reducing specificity or sensitivity
False-positive results	
LBBB, prior cardiac surgery (e.g., myectomy)	Reduced or abnormal septal excursion with normal septal thickness
Right ventricular pacing	Apical WMA
Nonischemic cardiomyopathy	Regional WMAs (exact cause unknown)
Hypertensive response to exercise (SBP > 220 mm Hg, DBP > 110 mm Hg)	Nonischemic WMAs and/or LV dilation
Overinterpretation	Observer bias may result in a lower threshold for calling a positive study; it is important to be blinded
Basal inferior or septal WMA	Areas most likely to be overcalled because of reduced excursion due to annular tethering effects
Poor image quality	
False-negative results	
Single-vessel disease	More likely to have subtle, rapidly resolving WMA than multivessel disease
Inadequate level of stress (more likely with β -blockers)	Important to stress maximally; reach at least 85% of age-predicted maximum heart rate
LV cavity obliteration (more likely to occur with dobutamine)	Makes segmental wall motion analysis difficult
Left circumflex disease	Lateral wall dropout; more likely to miss ischemia
Delay in capturing images after maximal stress	
Poor image quality	

DBP, diastolic blood pressure; LBBB, left bundle branch block; LV, left ventricular; SBP, systolic blood pressure; WMA, wall motion abnormality.

2. **LV cavity dilation and a decrease in global systolic function are not considered adjunctive diagnostic criteria in dobutamine SE.** The LV cavity may not dilate, and global systolic function may improve with dobutamine despite new WMAs due to severe CAD.
3. Interpretation of results obtained from **dipyridamole or adenosine SE** requires detection of a new or worsening regional WMA during the infusion. There is only a mild increase in cardiac contractility during vasodilator stress.
- E. **Reproducibility.** The person who interprets the images must be well trained to develop an acceptable level of accuracy and must interpret an adequate number of studies on a regular basis to maintain accuracy. Concordance within centers is generally good; however, concordance between different centers may be < 80%, particularly with technically difficult studies and studies of patients with mild CAD.
- F. **Limitations.** The ability to interpret stress echocardiograms is mitigated by the image quality, the presence of arrhythmias, conduction abnormalities, respiratory

interference from hyperventilation, and difficulty in allowing for translational and rotational motion of the heart.

VI. DIAGNOSTIC ACCURACY. The **diagnostic accuracy of SE is superior to exercise electrocardiographic testing alone and similar to radionuclide perfusion techniques.** Reported sensitivities and specificities (using coronary arteriography as the gold standard) vary between studies, depending on the prevalence of disease in the study population, the angiographic definition of significant disease, and the criteria used for a positive test. Clinical factors such as age, cardiac risk factors, and symptoms that influence the pretest likelihood of CAD also influence sensitivity and specificity. For the overall detection of patients with CAD, **sensitivity ranges from 75% to 92%, depending on lesion severity, and specificity ranges from 64% to 100%.** As with other imaging methods, the sensitivity is less for the detection of single-vessel disease and greater for the detection of multivessel disease.

A. Exercise SE

1. **Comparison with exercise electrocardiographic testing.** Exercise electrocardiographic testing remains the first-line diagnostic test for CAD. However, **SE has greater diagnostic sensitivity and specificity**, which is predictable on the basis of the earlier occurrence of a systolic WMA before electrocardiographic changes or symptoms in the ischemic cascade (Fig. 49.1). Many factors limit the sensitivity of electrocardiographic testing alone to detect CAD (Table 49.1), and these subgroups should be considered for exercise electrocardiographic testing with an imaging modality.
2. **Comparison with myocardial perfusion scintigraphy**
 - a. Myocardial perfusion scintigraphy is based on the detection of a perfusion defect during maximal hyperemia, with reduced perfusion of areas subtended by significant coronary artery stenosis (> 50% stenosis). Perfusion abnormalities occur at an earlier stage in the ischemic cascade than do systolic WMAs, and nuclear scintigraphy should theoretically have a higher sensitivity than SE for CAD.
 - b. Studies using **single-photon emission computed tomography (SPECT) myocardial perfusion scintigraphy have demonstrated a sensitivity of > 90%, slightly higher than that for SE.** However, the **specificity of SE is superior to that of SPECT**, especially in cases with LV hypertrophy or left bundle branch block. The overall accuracy of SPECT and SE has been found to be similar in meta-analyses; the superior sensitivity of SPECT is balanced by the superior specificity of SE. The exception may be in women, where SE may be more accurate than SPECT, owing to less artifact from breast attenuation.
 - c. SE is **convenient** and **provides information on cardiac structure and function, and the results can be interpreted immediately**, with rapid feedback to the patient and referring physician. SE also **avoids exposure to radioactive tracers** and is substantially **less expensive than SPECT**.
 - d. SPECT allows for more objective interpretation, with quantification of perfusion abnormalities. It may also be slightly superior for patients on antianginal therapy when it is necessary to induce ischemia. SPECT appears to be more sensitive in the detection of single-vessel disease and may be superior in the detection of ischemia in the setting of resting WMAs, in which the recognition of worsening wall motion may be difficult. SPECT may also be superior in patients that have poor acoustic windows, for example, chronic obstructive pulmonary disease. **Local expertise, cost, exposure to radiation, and patient selection are all important factors in determining which imaging modality to use.**

B. Pharmacologic SE

1. **Dobutamine SE has a sensitivity ranging from 68% to 96% and a specificity of 80% to 85%**, similar to the values for exercise SE. **Vasodilator SE has a sensitivity of 52% to 92% and a specificity of 80% to 100%.** In general, the specificity of vasodilator SE is superior to that of other echocardiographic stress techniques. However, single-vessel disease is more difficult to detect with this technique.

2. **Myocardial perfusion scintigraphy.** Compared with dipyridamole SPECT, dipyridamole SE is believed to be less sensitive but more specific; however, few studies have compared the two tests in the same patients. As with exercise SE, dobutamine SE appears to be slightly less sensitive but more specific than SPECT.

VII. ASSESSMENT OF VIABILITY

- A. Myocardial contractility ceases when 20% or more of the transmural thickness is ischemic or infarcted. Dobutamine SE can be used to detect **viable myocardium**, whether stunned or hibernating. **Myocardial stunning** after MI is common, and it is characterized by viable nonischemic noncontracting myocardium. Patients with **chronic ischemia** may experience **myocardial hibernation**. Hibernating myocardium is characterized by viable chronically ischemic noncontracting myocardium.
- B. Dobutamine infusion may result in augmentation of regional myocardial function predictive of recovery of function after revascularization. This is important prognostically, as revascularization of hypoperfused but viable myocardium improves survival. A contractile response to dobutamine requires that at least 50% of the myocytes in a given segment are viable.
- C. Demonstration of a **biphasic response** to low-dose (5 to 10 $\mu\text{g/kg/min}$) dobutamine strongly suggests viable myocardium. A biphasic response is present when a **resting WMA improves in response to low-dose dobutamine and decreases in function at peak stress or post-stress**. The initial improvement reflects recruitment of contractile reserve and hence viability. Higher doses lead to subendocardial ischemia and worsened WMA. A biphasic response predicts eventual functional recovery of the myocardium after revascularization. A uniphasic response is less predictive of recovery, and a classic ischemic response is not predictive of the recovery of resting function. Because the biphasic response is the most reliable finding, the preference is to induce ischemia whenever possible by proceeding to maximal stress (40 $\mu\text{g/kg/min}$).
- D. **Myocardial wall thickness** is also an important marker of myocardial viability. When the wall thickness is **< 6 mm**, there is **a low likelihood of recovery of function**.
- E. **The negative predictive value of dobutamine SE for determining viability is lower than that of thallium stress-redistribution-reinjection SPECT and Flourodeoxyglucose (FDG)-PET scanning.** However, **the positive predictive value is greater.** Concurrent use of β -blockers can reduce the number of viable segments detected and the sensitivity of testing.
- F. **Assessment of myocardial perfusion with echocardiography.** Second-generation microbubble contrast agents are small in diameter and reliably traverse the myocardial microvasculature. The microbubbles are destroyed with ultrasound energy, and the rate of microbubble replenishment represents mean red blood cell velocity and myocardial perfusion. As contrast agents and detection algorithms improve, it is hoped that these techniques will allow real-time, noninvasive assessment of myocardial viability.

VIII. PROGNOSTIC ROLE OF STRESS ECHOCARDIOGRAPHY

- A. **Suspected or known chronic CAD.** The **major determinants of prognosis** in patients with chronic CAD are **LV function and the anatomic extent and severity of myocardial ischemia**. SE is an excellent modality for the evaluation of both.
 1. **Negative test result.** Perhaps the most important aspect of the prognostic literature is that **a negative test result portends an extremely low risk of subsequent cardiovascular events, as evidenced by an event rate of < 1%/y for the subsequent 4 to 5 years.** However, the risk is slightly higher in patients with diabetes or chronic kidney disease.
 2. **Presence of ischemia.** Abnormal findings during SE indicate elevated risk for future cardiac events. Patients at intermediate risk for CAD who have abnormal SE findings have a 1-year cardiac event (i.e., MI, percutaneous coronary intervention, coronary

artery bypass grafting, or death) rate of 10% to 30%. However, this information needs to be integrated with other stress data (i.e., exercise capacity, hemodynamic responses to exercise, heart rate recovery, chronotropic index, Duke treadmill score, and the type and extent of WMA). Electrocardiographic changes and hypotension are relatively insensitive measures of ischemia during dobutamine SE. However, from the prognostic standpoint, the development of echocardiographic evidence of ischemia with dobutamine is analogous to its development during exercise.

3. **Presence of nonviable myocardium.** In patients with the same pretest probability of disease, those with evidence of nonviable myocardium during SE have higher rates of cardiac events than those with normal SE findings, but they have fewer events than those with evidence of ischemia during SE. Heart failure is a more common end point among the group of patients with nonviable myocardium.
- B. **Post-myocardial infarction.** High-risk patients after acute MI are routinely identified by age, recurrent angina, LV failure, and shock. In addition, echocardiographic features predicting outcome after MI include LV ejection fraction, the extent of resting WMAs, inducible ischemia (detected as stress-induced WMA), and the amount of viable myocardium. All of these may be identified using SE, and several large studies (most with pharmacologic stressors) have gathered prognostic data using SE in patients post-MI.
- C. **Noncardiac surgery**
 1. Preoperative evaluation studies have been predominantly conducted with pharmacologic stress agents, primarily dobutamine. However, exercise SE should be considered if possible. A low ischemic threshold during stress (ischemia at heart rate < 70% APMHR) is the strongest predictor of perioperative cardiac events.
 2. The predictive value of a positive test ranges from 7% to 25% for hard events (i.e., MI or death). The negative predictive value ranges from 93% to 100%. Only a few studies have compared SE and SPECT for the prediction of perioperative cardiac events. A meta-analysis concluded that the tests had comparable levels of accuracy, but the cost features weighted in favor of SE.
- D. **Cardiac transplantation.** Transplant vasculopathy is a major cause of mortality after cardiac transplantation. Despite some promising data, SE appears to lack both sufficient sensitivity and specificity to be a viable alternative to routine angiography as a screening method.
- E. **Reading beyond wall motion.** Important prognostic information can be obtained beyond traditional wall motion analysis. Ischemic heart disease may cause subclinical **diastolic dysfunction**. **Left atrial enlargement** correlates with the chronicity and severity of diastolic dysfunction. A normal resting left atrial volume index (< 28 mL/m²) is strongly predictive of a normal stress echocardiogram. **Right ventricular dysfunction** is a significant predictor of events, independent of LV ischemia or ejection fraction.

IX. DIASTOLIC STRESS ECHOCARDIOGRAPHY

- A. In many patients, “diastolic” heart failure is the dominant form of dysfunction, without any detectable systolic dysfunction at rest or during stress. The **transmitral peak early diastolic velocity (E)** and the **mitral annulus early diastolic velocity (e')** are utilized to assess the diastolic dysfunction. In the presence of normal LV systolic function and volumes, an **E/e' ratio > 15 suggests elevated LV filling pressure and diastolic dysfunction**, whereas a ratio < 8 excludes diastolic dysfunction. The primary utility of diastolic SE is to evaluate patients in whom diastolic dysfunction is suspected but the resting echocardiogram is indeterminate (i.e., E/e' 8 to 15). Assessment for diastolic dysfunction should be completed during routine SE, as its presence and severity add to the negative prognostic value of resting or stress-induced systolic dysfunction.
- B. Exercise or adrenergic stress normally results in improved myocardial lusitropy (relaxation) to allow for better filling in a shorter amount of time. The tachycardia associated with exercise results in an abbreviated diastolic filling period and an increase in the transmitral peak E velocity. In healthy patients, both the transmitral

peak E velocity and the mitral annulus early diastolic velocity increase with exercise, and the E/ \dot{e} ratio is not changed. However, **in patients with diastolic dysfunction, the mitral annulus early diastolic velocity is minimally affected by the change in preload caused by exercise and the E/ \dot{e} ratio increases.**

- C. Assessment of diastolic dysfunction can be difficult at rest and is even more so with stress. Exercise SE is optimally performed using **supine bicycle ergometry**, as it allows for the acquisition of Doppler recordings during exercise. However, evaluation is routinely performed using treadmill exercise or dobutamine. Tachycardia may result in fusion of the transmitral E and A velocities at peak stress, making the tracings impossible to interpret. Therefore, Doppler assessment of the mitral inflow velocities should be assessed at rest, during exercise, and in recovery if possible.

X. STRESS ECHOCARDIOGRAPHY IN NONISCHEMIC CARDIAC DISEASE. SE can be used to evaluate the functional significance of a variety of valvular lesions as well as hypertrophic cardiomyopathy. SE is especially helpful when there is a discrepancy between clinical symptoms and the assessment of valve severity at rest.

A. Aortic stenosis

1. Exercise testing is contraindicated (ACC/AHA class III recommendation) in patients with symptomatic AS. In asymptomatic patients, exercise testing may be considered (ACC/AHA class IIb recommendation) to elicit exercise-induced symptoms and abnormal BP responses.
2. Dobutamine SE is reasonable (ACC/AHA class IIa recommendation) in the diagnostic evaluation of patients with **low-flow/low-gradient AS**, defined as Doppler-derived aortic valve area $< 1 \text{ cm}^2$ and mean gradients $< 30 \text{ mm Hg}$. In these patients, **dobutamine is used to assess both the severity of AS and the presence of contractile reserve.**
3. In severe AS, low-dose ($20 \text{ }\mu\text{g/kg/min}$) dobutamine infusion results in increased cardiac output with a parallel rise in the mean transvalvular gradient. Provided the calculated aortic valve area remains $< 1 \text{ cm}^2$, **an increase in the mean transvalvular gradient to a value $> 30 \text{ mm Hg}$ or velocity $> 3.5 \text{ m/s}$ is consistent with severe AS.** If dobutamine infusion results in an increase in the valve area (typically to $> 1 \text{ cm}^2$) with little change in the gradient, it is likely that LV dysfunction rather than AS is the critical problem, and aortic valve replacement is unlikely to be beneficial.
4. Dobutamine SE is also used to identify **contractile reserve** in patients with low-flow/low-gradient AS. Contractile reserve is defined as $> 20\%$ increase in stroke volume with dobutamine infusion. Lack of contractile reserve is associated with poorer prognosis with either medical or surgical therapy.

- B. **Mitral regurgitation.** In asymptomatic patients with severe MR, exercise SE is reasonable (AHA/ACC class IIa recommendation) to assess exercise tolerance and the effects of exercise on pulmonary artery pressure and severity of MR. SE can help predict latent LV dysfunction in patients with normal baseline LV systolic function, severe MR, and minimal or no symptoms. An increase in the LV cavity size or decrease in LV ejection fraction at peak stress suggests latent LV dysfunction and an increased risk of LV dysfunction after valve repair.

- C. **Mitral stenosis.** Exercise SE should be performed (ACC/AHA class I recommendation) to assess the hemodynamic response of the mean gradient and pulmonary artery pressure in patients with mitral stenosis when there is a discrepancy among resting Doppler echocardiographic findings, clinical findings, symptoms, and signs. An increase in the mean transmitral pressure gradient $> 15 \text{ mm Hg}$ and pulmonary artery systolic pressure $> 60 \text{ mm Hg}$ are indications to consider percutaneous valvotomy.

- D. **Hypertrophic cardiomyopathy.** In patients with hypertrophic cardiomyopathy and high resting left ventricular outflow tract (LVOT) gradients, routine exercise testing is not performed owing to increased risks of arrhythmias and hypotension. Exercise SE provides valuable information, including exercise hemodynamics and the inducibility of LVOT, worsening of mitral regurgitation, and provokable

gradients in patients that are asymptomatic at rest. Although these patients may have only mild to moderately elevated resting LVOT gradients, using SE to identify elevated provokable gradients may help explain their exertional symptoms and quantify their exercise tolerance.

ACKNOWLEDGMENTS: *The author thanks Drs. Matthew Deedy, Patrick Nash, and Ryan Daly for their contributions to prior editions of this chapter.*

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Testing for Viable Myocardium

I. INTRODUCTION. Patients with left ventricular (LV) dysfunction secondary to coronary artery disease (CAD) have significant morbidity and mortality. Given the prognostic implications of poor ventricular function, it is imperative to identify any reversible myocardial dysfunction that may improve with revascularization.

II. DEFINITIONS

A. Viable myocardium is defined as myocardium that demonstrates abnormal function at rest and improves with revascularization.

1. From a pathophysiologic standpoint, chronically reduced perfusion leads to cellular changes that ultimately cause irreversible myocyte dysfunction.
2. Biopsies of myocardium reveal a spectrum of fibrosis and sarcomere loss that correlates with the likelihood of recovery of function. Several studies have found that once fibrosis is found in more than 35% of the myocardium, the likelihood of recovery of function is low.
3. **Stunning** refers to transient myocardial dysfunction, which is often caused by abrupt cessation of flow typical of an acute coronary occlusion.
4. Myocardial **scar** from cellular necrosis is irreversible and does not improve with revascularization.

B. Hibernation occurs when viable myocardium has altered its metabolism and thus reduced its contractile function as a mechanism to cope with chronically inadequate blood supply (chronic stable angina) or repetitive ischemic injury.

III. CLINICAL PRESENTATION. Ischemia, stunning, hibernation, scarring, and normal myocardium may coexist in the same patient. Unfortunately, clinical symptoms are unreliable in determining if a patient has viable myocardium, as often patients experience no symptoms in the face of considerable LV dysfunction and ischemia.

IV. TREATMENT OPTIONS. It has been demonstrated that revascularization of viable myocardium improves quality of life and survival. As medical and surgical technology improves in the field of cardiovascular medicine, it is important to accurately identify patients who will benefit from revascularization.

- A. Thrombolytic therapy or emergency percutaneous revascularization** is used in the setting of an acute thrombotic occlusion to restore normal blood flow and hopefully to minimize cellular damage.
- B. Revascularization procedures**, such as coronary artery bypass grafting and percutaneous transluminal coronary angioplasty, may improve regional and global LV systolic function caused by significant CAD. The presence and extent of viable myocardium have been demonstrated as a marker for patients who will do significantly better with revascularization than with conventional medical care.
- C.** It is notable that patients with nonviable myocardium have similar outcomes with medical therapy as with revascularization.

- D. Because not all patients benefit from revascularization procedures, the identification and referral of patients who will derive benefit are important to reduce costs and morbidity with the associated procedures. The goal, therefore, is to reliably identify patients who will benefit from revascularization and subsequently refer these patients for appropriate intervention.

V. TECHNIQUES TO ASSESS VIABILITY (Fig. 50.1). Assessment of myocardial viability is indicated in patients with CAD and resting LV dysfunction who are eligible for revascularization. Coronary angiograms provide information about anatomy and feasibility of revascularization but do not predict recovery of function. Resting echocardiography provides information regarding overall LV function and segmental wall motion abnormalities but does not address recovery of function with revascularization techniques. Single photon nuclear imaging techniques (single photon emission computed tomography, SPECT), positron emission tomography (PET) with a metabolic agent, dobutamine echocardiography, contrast echocardiography, and, more recently, delayed-enhancement magnetic resonance imaging (MRI) have been identified as techniques that can distinguish viable myocardium from nonviable myocardium. Each technique exploits a separate property of dysfunctional myocardium to determine the potential for recovery of function after revascularization. The test that is used often depends on the strengths and preference of each medical center, although an approach based on the individual patient would be preferable.

A. Single photon emission computed tomography. SPECT is the most common technique used in the United States to identify viable myocardium. This technique has been successful because thallium 201 and technetium 99m radiopharmaceuticals act as perfusion agents that are only taken up by viable tissue. The long half-lives of these agents allow for regional distribution, which makes them feasible to use in medical centers without a generator or cyclotron. In addition, stress SPECT protocols (exercise or pharmacologic) are frequently used to assess for ischemia, which makes this technique cost-effective in a busy clinical center. Routine studies also include gated imaging analyses that provide further information regarding LV function and wall motion assessment, which are important in the evaluation of viability.

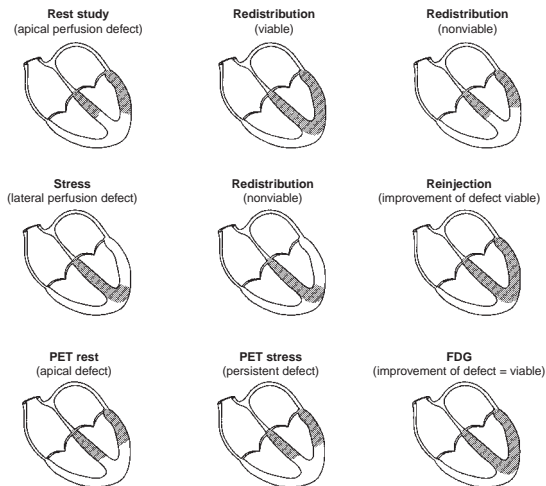


FIGURE 50.1 Viability testing.

FDG, 18F-fluorodeoxyglucose scanning

1. **Thallium 201** is a potassium analogue that utilizes the Na^+/K^+ -ATPase active cellular transport system for concentration in cells and relies on intact cells. This characteristic of thallium makes it useful for the identification of viable cells as opposed to necrotic cells. Uptake of thallium is also dependent on regional myocardial perfusion.
 - a. Thallium 201 has a relatively long half-life (73 hours), which means that a small dose (2 to 4 mCi) must be used. It emits x-rays from 68 to 80 keV (94% abundant) and γ -rays at 135 and 167 keV (10% abundant). There is a linear relationship between blood flow and uptake of thallium at rest, which is maintained with exercise making it a reliable indicator of perfusion.
 - b. **Redistribution** of thallium between the intracellular and intravascular spaces begins to occur after the first pass of thallium. It is recognized that with time, initial defects on thallium imaging improve. This is thought to be related to the accumulation of tracer in hypoperfused areas over time as well as rapid washout in normally perfused areas. On the basis of these principles, several protocols have been used to identify viable myocardium.
 - (1) **Rest/redistribution thallium** imaging involves imaging 30 to 60 minutes after an initial injection followed by reimaging 4 hours later. Defects on the initial images that improve in 4 hours are considered to represent areas of viable myocardium. This protocol does not address ischemia and has been proven to be less sensitive for detecting viable myocardium than other protocols using thallium or PET with 18F-fluorodeoxyglucose (FDG).
 - (2) **Stress/redistribution** imaging uses pharmacologic or exercise-induced stress with subsequent thallium injection and imaging, immediately followed by reimaging 4 hours later. Myocardium that is not perfused with stress or rest is considered to be scar. Myocardium that has a defect with stress but that improves on rest images is considered to be ischemic and viable. This protocol can identify ischemic viable myocardium, but it also shows lower sensitivity than other protocols, as many of the defects that do not improve at 4 hours may contain viable tissue. Imaging 24 hours after stress in a search for “late redistribution” improves sensitivity in the detection of viability but has low specificity and may be inconvenient. However, blood levels of thallium 201 may still be too low to be redistributed and picked up by viable myocardium. This led to the development of reinjection protocols mentioned later in this chapter.
 - (3) **Stress/redistribution/reinjection** protocols involve the reinjection of 1 mCi of thallium with subsequent reimaging of the patient. This protocol is designed to increase the sensitivity by increasing the blood levels of thallium. It was shown that 50% to 70% of “scarred myocardium” after 4-hour redistribution imaging was actually viable, as demonstrated by this technique. Typically, reinjection of thallium and repeated imaging is performed immediately after the redistribution images or several hours after the initial stress images, followed by redistribution imaging 18 to 24 hours later. Sensitivity does not differ significantly between these two techniques. Scar is considered to be myocardium that has a defect on the stress images and does not improve upon reinjection and reimaging. Viable myocardium is indicated by uptake of tracer on reinjection in segments where no uptake occurred with stress.
2. **Technetium 99m-labeled radiopharmaceuticals** rely on mitochondrial function, sarcolemmal integrity, and intact energy production pathways for cellular accumulation.
 - a. **Technetium characteristics.** Technetium 99m compounds have a shorter half-life (6 hours) than thallium, which allows for the administration of

- b. Redistribution of technetium compounds is significantly less than that for thallium, making it relatively unhelpful as an aid in detecting viability.

3. **Quantitation** of SPECT imaging has been found to be a more accurate method to identify high- and low-risk populations than qualitative analysis. Quantification of perfusion has been proven to be an accurate predictor of recovery of function and superior to qualitative measurements at providing clinically useful information about future risk.
4. **Diagnostic accuracy**
 - a. Multiple studies have been performed comparing the various thallium protocols versus PET with FDG as the gold standard. Typically, sensitivity improves as one goes from redistribution to reinjection/redistribution and finally quantitative analysis of reinjection/redistribution. Semiquantitative analysis of stress/redistribution/reinjection has good concordance with PET.
 - b. In the prediction of functional improvement after revascularization, rest/redistribution thallium scans (sensitivity 90% and specificity 54%) and stress/redistribution/reinjection thallium scans (sensitivity 86% and specificity 47%) have been found to be less reliable. Regions that demonstrate < 60% regional thallium uptake on redistribution have a very low chance of recovery.
 - c. Unfortunately, attenuation and patient artifact frequently make SPECT thallium images difficult to interpret. In addition, methods for quantification have not been standardized across medical centers.
 - d. **Quantification** of sestamibi has compared favorably with that of thallium, with redistribution in the prediction of recovery of function after revascularization. Several other technetium compounds used for the assessment of viability have been tested (Tc 99m tetrofosmin, Tc 99m teboroxime, Tc 99m furifosmin, and Tc 99m NOET). None of these other agents has had significant use except for ^{99m}Tc-NOET, which has similar redistribution kinetics to that of thallium and may be a useful agent in the future. Sestamibi has a limited role in viability assessment owing to its cost.
- B. **PET** in conjunction with a metabolic agent, usually FDG, has been considered the gold standard for assessment of myocardial viability. PET uses positron-emitting isotopes capable of releasing two high-energy (511 keV) photons at an angle of 180° from each other. The PET camera can detect these higher energy rays through coincidence counting. As a result, PET provides higher temporal and spatial resolution than SPECT, which translates into a higher quality image. Additional features of PET include quantification of the following:
 1. Practical issues, including the cost of a PET camera and the short half-life of the several of the cyclotron-produced radiotracers, limit the use of PET to specialized medical centers.
 2. Unlike SPECT, PET uses separate agents to measure perfusion and viability.
 3. **Perfusion** agents commonly used in PET imaging include rubidium 82, nitrogen 13 ammonia, and oxygen 15 water.
 - a. **Rubidium 82** is a generator-produced potassium analogue that relies on intact cellular functioning for its uptake and distribution. Hence, rubidium 82 is washed out of necrotic cells and trapped in viable cells.
 - b. **Nitrogen 13 ammonia** is cyclotron-produced radiotracer and also relies on intact cellular functioning for its uptake and distribution. This is the most commonly used perfusion agent in PET, and it can be used to quantify blood flow and assess for myocardial viability.

- c. **Oxygen 15 water** is a freely diffusible agent that has been used to quantify blood flow. Blood flow < 0.25 mL/g/min within a region of myocardium is correlated with regions of scar. Unfortunately, intermediate blood flow ranges have not been reliable in predicting recovery of function, which makes this technology less useful for quantifying viability. Oxygen 15 water has also been used to create a perfusable tissue index that has been shown to improve the accuracy in the assessment of viable myocardium but has not been utilized by many centers.
4. **Metabolic agents** used in PET include FDG, carbon 11 acetate, and carbon 11 palmitate. **FDG** (cyclotron-produced) has the most clinical data to support its use. It has a long half-life, which makes its transportation to regional medical centers more practical. FDG is taken up by viable cells and then phosphorylated so that it cannot be metabolized further. This effectively traps FDG in the myocardium. In normal myocardium, free fatty acids are preferentially used. During periods of ischemia, metabolism is altered so that primarily glucose is utilized. The limitation of FDG has been in diabetics with impaired cellular uptake of glucose, where approximately 10% of studies are difficult to interpret owing to poor tracer uptake.
5. The combination of perfusion and metabolic tracers gives three possible interpretations:
 - a. Normal perfusion is indicative of viability on its own and does not require specific assessment of metabolism.
 - b. Reduced perfusion in myocardial segments with intact metabolic function as evidenced by the uptake of FDG is termed flow–metabolism mismatch and is indicative of hibernating, viable myocardium (Fig. 50.2).
 - c. Impaired FDG uptake combined with reduced perfusion (flow–metabolism match) is indicative of myocardial scar (Fig. 50.2).
6. **Diagnostic accuracy.** PET-FDG and cardiac MRI are considered the most reliable tests of myocardial viability. Image quality with PET is better than that with SPECT, and myocardial metabolism may be assessed directly with FDG. The sensitivity and specificity of PET in predicting functional improvement in myocardial segments after revascularization are 71% to 100% and 38% to 91%,

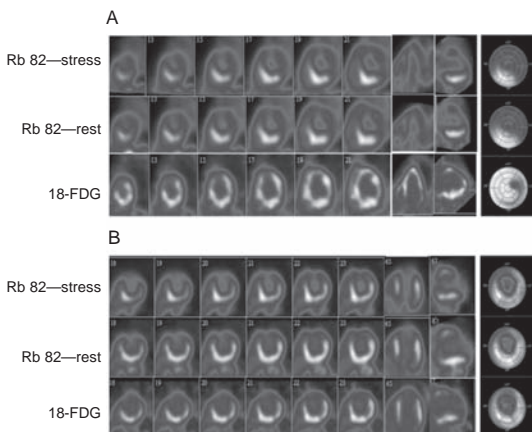


FIGURE 50.2 Rubidium PET followed by FDG PET: Patient **A** showing metabolism mismatch and is indicative of hibernating, viable myocardium. Patient **B** showing impaired FDG uptake combined with reduced perfusion (flow–metabolism match) is indicative of myocardial scar.

respectively. PET has been shown to predict low surgical risk in patients with LV dysfunction and viability, improvement in exercise capacity with revascularization, and benefit from revascularization over medical therapy.

C. Dobutamine echocardiography has proven to be a reliable predictor of recovery of function after myocardial revascularization.

1. **Protocol.** Viability studies with dobutamine echocardiography use low doses of dobutamine starting as low as 5 $\mu\text{g/kg/min}$ and slowly increasing the dose at 3-minute intervals up to 40 $\mu\text{g/kg/min}$ for the development of other end points, such as target heart rate and symptoms. Imaging is performed throughout the study at each level of dobutamine infusion. Accurate, consistent results are contingent on the acquisition of excellent images for interpretation and on an experienced reader to interpret the study.
2. **Pathophysiology.** Dobutamine echocardiography exploits the inotropic effect of dobutamine at low doses on viable myocardium. This improvement in function and wall thickening is referred to as contractile reserve. In viable myocardium, with increasing doses of dobutamine, myocardial oxygen consumption increases, and ischemia develops with worsening of wall motion abnormalities. Therefore, in viable myocardium a segment with reduction in wall thickening at rest demonstrates an improvement or even normalization of wall thickening upon infusion of low-dose dobutamine. At higher doses of dobutamine, wall thickening deteriorates and may revert to the baseline level or may be even more severely reduced than at baseline. This **biphasic response** during dobutamine echocardiography is thought to be the most specific sign of dobutamine echocardiography for predicting improvement in function in myocardial segments with revascularization and indicates segments with underperfused but viable tissue. Myocardial segments with impaired contraction at rest that do not improve upon infusion of dobutamine are considered to be scarred (nonviable). Those segments with impaired thickening at rest that show improvement in thickening upon dobutamine infusion but that do not show deterioration in thickening at higher doses of dobutamine infusion are considered to have a **uniphasic response**. A uniphasic response is seen in the setting of myocardial damage with subsequent reperfusion (i.e., an open artery without a flow-limiting stenosis) and is much less predictive of improvement after revascularization.
3. **Diagnostic accuracy.** Dobutamine echocardiography has good specificity for the detection of viability. Part of the high specificity is derived from the fact that echocardiography is the most common method of assessing postoperative improvement. In addition, improvement of hypocontractile myocardium in response to low-dose dobutamine is the defined end point that revascularization is trying to achieve, although it is less sensitive than cellular metabolic function as a marker of viability. Sensitivity and specificity for recovery of function are 84% and 81%, respectively.
4. **Limitations** of dobutamine echocardiography include difficulty in obtaining images in patients with poor ultrasound windows, interobserver variability, even among expert readers, provocation of ventricular arrhythmias with testing, and reduced sensitivity in comparison with nuclear imaging.

D. Cardiac MRI. Delayed-enhancement MRI using gadolinium-based agents given intravenously (0.2 mmol/kg) has been shown to reliably distinguish infarcted from viable myocardium. Unlike SPECT-based techniques, MRI poses no risk of ionizing radiation exposure.

1. **Pathophysiology.** Gadolinium-based contrast agents are extracellular compounds that, when injected intravenously, pass quickly through normal areas of myocardium. In scarred tissue, the interstitial space between collagen fibers is larger than in normal myocardium, causing a delayed “wash-in” of gadolinium contrast. The gadolinium then remains trapped in the scarred tissue, causing

a longer “washout” of gadolinium from the infarcted or fibrotic myocardium. Delayed-enhancement MRI takes advantage of this delayed wash-in and wash-out of gadolinium to detect fibrotic or scarred myocardium, which appear as hyperenhanced (bright) areas of myocardium on images taken 10 to 20 minutes after contrast injection.

2. In patients with ischemic heart disease, scarred or nonviable myocardium occurs in a coronary artery distribution. Scarring typically begins at the subendocardial surface and extends outward at a variable distance toward the epicardium. The **transmural extent of hyperenhancement** on delayed-enhancement images is then used to determine the viability of each myocardial segment. Segments with **0% to 25% transmural extent of hyperenhancement represent viable tissue** with mostly normal myocardium and minimal fibrosis. **Segments with 75% to 100% transmural extent of hyperenhancement represent scarred, nonviable myocardium.** Segments with 25% to 75% transmural extent are said to have intermediate viability, although in clinical practice the amount of viable tissue in adjacent myocardium is often taken into account when classifying these intermediate segments. Finally, the amount of hyperenhancement within a region can be correlated with segmental wall function and rest/stress perfusion to determine ischemia and viability.
3. The absence of significant hyperenhancement has been shown to correlate well with improvement in function, whereas hyperenhancement of more than 75% has been correlated with irreversible injury. Of interest to note, the mean transmural extent of hyperenhancement that predicted irreversibility was $41 \pm 14\%$ by MRI, which correlates with a biopsy series wherein 35% fibrosis predicted similar lack of improvement after revascularization (Fig. 50.3).
4. **Diagnostic accuracy.** Studies comparing different imaging modalities for viability have shown superior sensitivity and specificity for MRI compared with SPECT and similar sensitivity with slightly improved specificity compared with PET. The main advantage of MRI is its ability to delineate the transmural extent of infarction, owing to its better spatial and contrast resolution. The pattern of hyperenhancement on MRI can also be used to identify nonischemic causes of cardiomyopathy.
5. **Limitations.** MRI is generally contraindicated in patients with implanted ferromagnetic objects (e.g., pacemakers, implantable cardioverter–defibrillators [ICDs], and ferromagnetic cerebral aneurysm clips), although some centers will image selected patients with permanent pacemakers/ICDs under careful electrophysiologic evaluation. Gadolinium is contraindicated in patients with chronic kidney disease (glomerular filtration rate < 30 mL/min), particularly in those

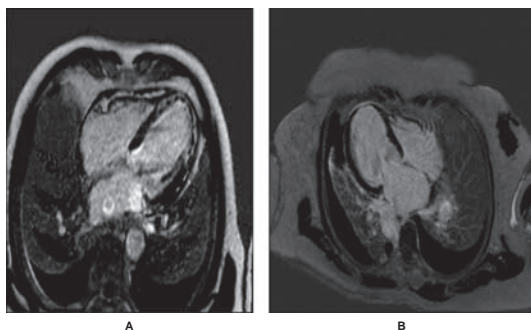


FIGURE 50.3 Late gadolinium-enhanced MRI: Both patients **A** and **B** have extensive akinesia in LAD territory; however, patient **A** has more extensive scar ($> 50\%$ in multiple segments) than patient **B** and is less likely to have LV function recovery post revascularization.

undergoing dialysis, owing to a small but important risk of nephrogenic systemic fibrosis (see Chapter 51). Finally, image quality may be compromised in patients unable to comply with breath-holding for the study (10 to 12 seconds each) and severe claustrophobia, as well as in patients with arrhythmias or frequent ectopy.

VI. CHOICE OF TECHNIQUE. Cost, clinical expertise, and access to radioisotopes are all issues that affect the appropriateness of each imaging technique. SPECT thallium and dobutamine echocardiography are significantly less expensive than PET and MRI, but they require significant clinical experience for appropriate data collection and interpretation. Both PET and cardiac MRI are robust techniques for the assessment of viability, but their use may be limited due to cost and availability, and, for MRI, the presence of patient's contraindications to MRI. The choice of technique is ultimately determined by local expertise and access to the appropriate technology. The recently published STICH (Surgical Treatment for Ischemic Heart Failure) viability trial failed to demonstrate a significant interaction between myocardial viability and medical versus surgical treatment with respect to mortality. These findings are most likely explained by improved modern-day medical therapy; however, there were several limitations of this trial which should be noted. Although the main STICH trial was a randomized controlled trial, the STICH viability substudy was not randomized. It was an observational study on almost half of all the main STICH trial patients who managed to get a viability study. Furthermore, viability testing in the trial was performed by using SPECT, thallium, and dobutamine only, and more robust techniques of cardiac MRI and FDG PET were not used.

VII. WHO SHOULD GET A VIABILITY TEST? Patients who are most likely to benefit from viability testing (preferably by cardiac MRI or FDG PET) are those with high operative risk, where presence or absence of viability may influence the management strategy. Viability can also be useful in choosing the optimal revascularization strategy (PCI vs. CABG) in patients with multivessel disease. Viability testing should not be performed in patients where it is unlikely to change management, such as in a young patient with angina, good distal target vessels, and minimal comorbidities.

ACKNOWLEDGMENTS: *The author thanks Drs. Anne Kanderian, Benjamin Atkeson, and C. Patrick Green for their contributions to earlier editions of this chapter.*

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CHAPTER

51

João L. Cavalcante

Cardiovascular Magnetic Resonance Imaging

- I. **INTRODUCTION.** Cardiovascular magnetic resonance imaging (CMRI) has undergone rapid developments over the last two decades and is now an important imaging technique of the heart and great vessels. Advantages of CMRI include its large field of view, high spatial and temporal resolution, and ability to do tissue characterization. In contrast to nuclear imaging and cardiac computed tomography (CT), magnetic resonance imaging (MRI) does not involve exposure to ionizing radiation. Applications of CMRI include acquisition of anatomic-quality still and cine images of the heart and great vessels in multiple planes, precise measurement of cardiac chamber volume and function, assessment of myocardial perfusion and fibrosis, quantification of blood velocity and flow, and noninvasive magnetic resonance angiography (MRA). As CMRI is not a “push-button” technique, clear communication between the ordering physician and the imaging staff is important, indicating the reason for the CMRI examination so that adequate pulse sequences and imaging planes are obtained aiming to answer the desired clinical question.

II. INDICATIONS. Common indications and components of the CMRI evaluation are listed in Table 51.1.

III. CONTRAINDICATIONS. Contraindications to CMRI are listed in Table 51.2.

IV. BASICS OF CARDIAC MRI

A. MRI Physics. Hydrogen is the most abundant atom in the body, and it is the excitation of hydrogen nuclei, often referred to as protons, that forms the basis for clinical MRI. Atoms behave like tiny bar magnets, aligning parallel to an external magnetic field while wobbling about the magnetic field at a certain frequency (precessional frequency) that creates the longitudinal magnetization. Application of a short radiofrequency (RF) pulse with the same precessional frequency as that of the atomic nucleus will cause excitation or resonance of the nucleus, temporarily changing its alignment within the magnetic field (transverse magnetization). However, this is an unstable state of higher energy. As the RF pulse is switched off, the spins quickly return to their resting state, i.e., aligned with the field, as this is energetically

TABLE 51.1 Cardiovascular Magnetic Resonance Imaging Indications and Applications

Indication(s)	Applications
Aortic disease	Aortic aneurysm morphology and size; acute aortic pathology (dissection, intramural hematoma, penetrating ulcer); coarctation of the aorta; branch vessel disease; evidence of vasculitis; postoperative graft stenosis, infection, or leak; assessment for aortic regurgitation or other associated pathologies
Ischemic heart disease	Ventricular volumes and function; myocardial scar and viability; quantification of mitral regurgitation; assessment for LV aneurysm, thrombus, VSD, and other complications
Nonischemic cardiomyopathies	Ventricular volumes and function; myocardial wall thickness; LV outflow tract obstruction in hypertrophic cardiomyopathy; presence and patterns of myocardial scar/fibrosis; assessment for myocardial iron deposition in suspected hemochromatosis; quantification of mitral regurgitation; evaluation for ARVD in patients with ventricular arrhythmias or syncope
Pericardial disease	Pericardial effusion; pericardial thickening with or without calcification; pericardial tethering; signs of constrictive physiology including conical/tubular deformity of the ventricles, diastolic septal bounce, early cessation of diastolic filling, and dilated IVC
Congenital heart disease	Anatomic definition; ventricular volume and function; valve morphology and function; shunt calculation; assessment for anomalous origin of the coronary arteries; anomalies of the aorta, pulmonary arteries, and systemic and pulmonary veins
Valvular heart disease	Valve morphology; regurgitation and/or stenosis etiology and severity; ventricular size and function
Cardiac masses	Size and extent of mass; tissue characterization
Pulmonary veins	Pulmonary vein anatomy and stenosis; cardiac anatomy and function

ARVD, arrhythmogenic right ventricular dysplasia; IVC, inferior vena cava; LV, left ventricular; VSD, ventricular septal defect.

TABLE 51.2 Contraindications to Cardiovascular Magnetic Resonance Imaging

Specific devices	Special issues
Cerebral aneurysm clips	Certain cerebral aneurysm clips pose a danger due to potential for displacement when exposed to a magnetic field. Aneurysm clips classified as “nonferromagnetic” or “weakly ferromagnetic” are safe.
Cardiac pacemakers and ICDs	<p>The presence of a pacemaker/defibrillator is a strong relative contraindication to MRI owing to several potential problems, including (1) movement, (2) malfunction, (3) heating induced in the leads, and (4) current induced in the leads. In addition, artifact from the leads will often cause significant image degradation.</p> <p>FDA has recently approved the first MRI-safe pacing system (Revo MRI by Medtronic, Inc.) that allows patients to undergo, for example, brain and knee MRI scans. Currently it is not safe for the area of coverage to include the chest, although ongoing work is being done toward that goal.</p>
Cardiovascular catheters	Catheters with conductive metallic components (e.g., pulmonary artery catheters) have the potential for excessive heating. Hence patients with such devices should not undergo MRI.
Cochlear implants and hearing aids	Most types of implants employ a strong magnet or are electronically activated. Consequently, MRI is contraindicated because of potential injury or damage to the function of these implants. External hearing aids can and should be removed before the MRI procedure.
Intravascular coils, stents, and filters	These devices typically become incorporated securely into the vessel wall within 6–8 wk after implantation; hence, most are considered MRI safe. However, specific information on the type of device should be obtained before MRI is planned (www.mrisafety.com). Intracoronary stents have been shown to be safe during MRI, even when performed on the day of implantation, although many stent manufacturers recommend waiting 6–8 wk.
ECG electrodes	MR-safe ECG electrodes are strongly recommended to ensure patient safety and proper ECG recording.
Foley catheters	Certain Foley catheters with temperature sensors have the potential for excessive heating. They are generally safe if positioned properly and disconnected from the temperature monitor during MRI.
Heart valve prostheses	All types of heart valve prostheses have been shown to be safe during MRI. However, prosthetic material may lead to image artifacts.
Metallic foreign bodies	All patients with a history of injury with metallic foreign bodies such as a bullet or shrapnel should be thoroughly evaluated, as serious injury may result from movement or dislodgement of the foreign body.
Metallic cardiac occluders (e.g., management of PDA, ASD, or VSD)	<p>MRI is safe for nonferromagnetic devices immediately after implant.</p> <p>Weakly ferromagnetic devices are safe from approximately 6–8 wk after placement, unless there is concern about retention of the device.</p>
Retained epicardial pacing wires	MRI in patients with retained epicardial pacing wires after cardiac surgery appears safe. Retained transvenous pacing wires are a contraindication to MRI.

ASD, atrial septal defect; ECG, electrocardiogram; ICD, implantable cardioverter–defibrillator; MR, magnetic resonance; MRI, magnetic resonance imaging; PDA, patent ductus arteriosus; VSD, ventricular septal defect.

the most favorable situation. The newly established transverse magnetization starts to disappear (a process called transversal relaxation), and the longitudinal magnetization grows back to its original size (a process called longitudinal relaxation). During this process, an RF signal is generated, which can be captured by the receiving coil and readily measured. This process constitutes the underlying principle of MRI.

The signal generated by an excited proton is dependent on its molecular environment, such that the magnetic resonance (MR) signal from a hydrogen atom in blood can be discriminated from the MR signal from a hydrogen atom in fat or other tissue types. An MRI machine, therefore, includes a strong magnet that creates a continuous magnetic field and RF coils for transmitting the excitation pulses and receiving the radio signals generated by the excited protons. Application of predictable variations or “gradients” in the magnetic field, using gradient coils within the magnetic bore, allows three-dimensional (3D) spatial localization of each signal. The raw data are initially mapped in “k-space” before a Fourier transformation to generate the final MRI image.

- B. T1, T2, and image contrast.** The rate of relaxation of an excited proton along the longitudinal axis (i.e., the direction of the external magnetic field) is described by its T1 time, whereas the transverse axis is described by its T2 time. T1 and T2 times depend on the molecular environment of the protons (intrinsic to the tissue characteristics) and the magnetic field strength. T1 and T2 relaxation times of different tissues are important determinants of image contrast and, although not measured directly, images can be either T1 or T2 “weighted” to facilitate tissue characterization.
- C. Issues specific to CMRI.** Cardiac and respiratory motion poses significant challenges to CMRI. In contrast to echocardiography, which is based on real-time imaging, CMRI sequences usually acquire a single image over several heart beats to optimize the spatial and temporal resolution. It is, therefore, necessary to gate images to the cardiac cycle with either an electrocardiographic or pulse signal. Electrocardiographic gating is usually retrospective, although prospective gating is sometimes useful, particularly in patients with arrhythmias. Respiratory motion is typically negated by performing breath-holds during the examination. In patients who are unable to maintain a breath-hold, averaging multiple MR signals may help to decrease the noise created by respiratory motion, at the expense of increasing the examination time by a factor of the *number of signals averaged*. Respiratory navigator sequences that coordinate imaging with a particular phase of diaphragmatic and hence respiratory motion are also effective, and they are typically used for pulse sequences that are too long for a single breath-hold, such as free-breathing whole-heart 3D coronary MRA sequences. Finally, real-time imaging using newer ultra-fast pulse sequences can be used in the absence of electrocardiographic or respiratory gating, at the expense of a significant decrease in temporal and spatial resolution.
- D. CMRI pulse sequences and applications**
- 1. Spin echo.** Spin-echo sequences are characterized by a refocusing RF pulse after delivery of the initial excitation pulse. Rapidly flowing blood appears dark, hence they are also known as “black-blood” sequences. Spin-echo sequences provide still images, which are typically used for anatomic delineation of the heart and great vessels owing to their excellent tissue contrast and high signal-to-noise ratio (SNR). They are relatively insensitive to magnetic field inhomogeneities and artifacts related to ferromagnetic objects such as sternal wires and prosthetic heart valves. Turbo spin echo is a newer technique that provides faster acquisition times than standard spin echo does. The main disadvantage of spin-echo sequences is the relatively long time it takes to acquire an image, making them more susceptible to motion artifacts and unsuitable for cine imaging.
 - 2. Gradient echo.** Gradient echo sequences are characterized by the use of refocusing gradients after the delivery of the initial excitation pulse. Rapidly flowing blood appears bright, hence they are also known as “bright blood” sequences. Gradient echo is a fast imaging technique that is relatively insensitive to motion artifacts,

- making it ideal for cine imaging. However, it has less tissue contrast and increased susceptibility to magnetic field inhomogeneities and ferromagnetic-related artifacts than spin-echo imaging but less than balanced steady-state free precession (B-SSFP). A variety of gradient echo sequences are widely used in CMRI for cine imaging, myocardial perfusion and scar assessment, coronary imaging, and MRA.
3. **Cine imaging.** The most widely used pulse sequence for cine imaging is a gradient echo sequence called balanced steady-state free precession (B-SSFP), which is characterized by high SNR, high image contrast between blood and myocardium, and low sensitivity to motion artifact. However, B-SSFP is relatively insensitive to blood flow and, therefore, can be suboptimal for imaging of valve dysfunction or intracardiac shunts, which can usually be better illustrated using other gradient echo pulse sequences, such as echo planar imaging or phase velocity mapping. In addition B-SSFP is also more susceptible to magnetic field inhomogeneities which can be problematic in patients with mechanical valves or other cardiac implants.
 4. **Myocardial tagging.** RF pulses can be applied before the excitation pulse to generate dark saturation lines or grids on cine images, which are then tagged to the myocardium and further used to assess myocardial deformation. The tags can be used to help qualitatively assess myocardial motion and pericardial tethering or to quantitatively measure myocardial strain.
 5. **Perfusion imaging.** Very fast gradient echo sequences are used for dynamic imaging of left ventricular (LV) myocardial perfusion during the first pass of a gadolinium contrast agent during rest and stress states. Fast gradient echo techniques are commonly used, such as fast low-angle shot or B-SSFP with a prepulse to null or darken the myocardium. Normally perfused myocardium shows an increase in signal intensity due to gadolinium contrast, whereas abnormally perfused areas remain dark or hypoperfused.
 6. **Delayed imaging.** Delayed hyperenhancement imaging for myocardial scar or fibrosis is performed 10 to 30 minutes after injection of gadolinium contrast using gradient echo sequences with an inversion recovery prepulse to null signal from the myocardium. **Areas of myocardial scar or fibrosis have a larger extracellular space with a greater accumulation and slower washout of gadolinium and, therefore, appear bright compared with dark, normal myocardium on delayed imaging.**
 7. **Phase-contrast velocity mapping.** The phase difference in the spin of protons in moving blood compared with nonmoving protons within a magnetic gradient is called the “spin phase shift” and is proportional to the velocity of the moving protons. A phase-encoded image is constructed, with the gray level of each pixel coded for velocity. Phase-contrast velocity mapping could be considered analogous to pulse wave Doppler echocardiography. It can be used to measure blood velocity and hence quantify cardiac output, shunts, and valve dysfunction. There are, however, limitations, given that the accuracy of this method is highly dependent on factors such as flow pattern, flow velocity, size, and tortuosity of the vessel. Flow-related signal loss can be a result of loss of phase coherence that can occur in cases of significant flow acceleration and even in higher orders of motion present in complex flow patterns.
 8. **Magnetic resonance angiography.** MRA of the great vessels typically involves a 3D fast gradient–echo acquisition after injection of gadolinium contrast. The image resolution is typically $2 \times 2 \times 3$ mm, making MRA an excellent option for imaging of large to intermediate size arteries, but less optimal for imaging of smaller vessels.
 9. **Parallel imaging.** A number of parallel imaging techniques make use of multiple receiving body coils to acquire extra data after each excitation pulse. This helps to decrease the imaging time and improve temporal resolution, but at the small relative cost of decrease in the SNR.
 - E. **Contrast agents.** A number of gadolinium chelates are used as contrast agents in clinical MRI. **Gadolinium significantly shortens the relaxation time of nearby**

protons, thereby increasing their signal intensity. These contrast agents are safe, with a low side-effect profile. Prevalence of adverse reactions is approximately 2% and includes transient headache, nausea, vomiting, local burning or cool sensation, and hives. Anaphylactoid reactions are extremely rare. Recently, gadolinium has been linked to a severe and rapidly progressive form of systemic sclerosis called **nephrogenic systemic fibrosis (NSF)**, which appears to be related to extracellular accumulation of gadolinium after its administration in patients with end-stage renal disease. The US Food and Drug Administration (FDA) has advised that **gadolinium contrast agents should not be administered to patients with a glomerular filtration rate of <15 mL/min. Caution should be exercised in patients with moderate or severe renal impairment.** Dialysis is only partly effective at filtering gadolinium and may not prevent development of NSF.

V. PRACTICAL CONSIDERATIONS

A. Safety

1. **Magnetic force.** Cardiac MRI scanners typically utilize powerful magnets of 1.5 to 3.0 T, several tens of thousands of times stronger than the earth's magnetic field (0.00005 T). Large or small ferromagnetic objects in the vicinity of the MRI magnet bore can become fast moving projectiles, which may cause severe injury to patients and/or damage the MRI scanner. A number of fatalities related to such events have been reported. Health-care professionals working in the vicinity of an MRI scanner require MRI safety training and should be vigilant to risk posed by patients and health-care professionals not familiar with the danger.
2. **Magnetic field gradients.** Switching of magnetic field gradients during a CMRI study produces high acoustic noise levels (up to 115 dB) and can also lead to peripheral nerve stimulation. The FDA has determined limits to the power of magnetic field gradients and noise exposure. Headphones and earplugs are recommended to prevent discomfort and hearing loss to patients and MRI staff in the vicinity of the scanner.
3. **Bioeffects of RF energy.** The majority of RF energy to the patient is dissipated as heat and is recorded as the specific absorption rate (SAR). One SAR equals 1 joule of RF energy per second per kilogram of body weight (i.e., watts per kilogram). The recommended SAR limit for the whole body is 4 W/kg.

B. Patient preparation

1. **Screening.** All patients should be screened for contraindications to MRI before the procedure (Table 51.2). Proper screening technique involves the use of a printed sheet and review of the completed form with the patient by an MR safety-trained health-care worker to verify the information.
2. **Patient size.** Although the maximum table load weight limit is fairly generous (~250 kg or 550 lbs), because of the fixed internal diameter of the magnet bore, very large patients may not fit within the MRI magnet. Typically, patients with a torso circumference of > 60 cm cannot be imaged. Discussion with the MRI technologist before scanning is recommended for specific recommendations related to your unit.
3. **Claustrophobia.** The enclosed space of the magnet poses problems for many patients, even those who do not have a history of claustrophobia. The study can usually be successfully completed with the help of clear communication with the patient before and during the procedure, presence of a friend or relative at the head of the MRI scanner, or light oral sedation (e.g., lorazepam 0.25 to 0.5 mg) 30 to 60 minutes before the procedure.

Early versions of open MRI scanners had low magnetic field strength, gave poorer image quality than most closed systems, and required longer examination times. Newer open scanners include machines with higher magnetic field strengths and improved image quality and could become important alternatives in patients with claustrophobia.

4. **Attire.** Patients should wear a cotton hospital gown with no metal snaps. All metal items, jewelry, and nylon undergarments should be removed for reasons of safety and possible image degradation.
5. **Body coil.** Phased array body coils are placed on the patient's torso over the imaging area of interest. These use several smaller coils to acquire RF signals simultaneously and to facilitate parallel imaging. Some of these coils, for example, enable performance of 3D cardiac cine exams with full-ventricle coverage in a single breath-hold. The net result is not only better image quality but also reduced exam time for the patient.
6. **Electrocardiogram (ECG) monitoring.** A good electrocardiographic tracing is essential for CMRI. Although three or four MRI-safe, nonmetallic electrodes are placed on the patient's chest, and a single lead signal is used to trigger or gate the MRI images, the magnetic field affects the electrocardiographic tracing by inducing a voltage created by ions flowing within blood vessels (magnetohydrodynamic effect). This voltage artifact is commonly superimposed in the ST segment (during the ejection of blood in systole), which increases its amplitude causing false QRS detection in certain algorithms. Use of vector cardiogram allows the R-R interval to be registered as a 3D spatial vector that varies in magnitude and direction throughout the cardiac cycle. Furthermore, the use of fiber optic cables (instead of carbon leads) has also decreased the potential ECG interference of RF pulses and/or gradient field switches.
7. **Emergencies.** MRI is not appropriate in patients who are clinically unstable because of difficulties monitoring and treating patients within the magnet bore. Although MRI-safe equipment is available, it is safer to prescreen the patient's clinical status and determine the need of the MRI study before initiating the scanning.
8. **Pregnancy.** There is insufficient evidence regarding the safety of MRI in pregnant patients. Current guidelines state that MRI may be used in pregnant patients where other forms of nonionizing imaging are inadequate or if the examination provides important information that would otherwise require exposure to ionizing radiation.
9. **Children.** CMRI may be necessary in pediatric patients with congenital and acquired cardiovascular disease. Typically, children younger than 8 years will require general anesthesia.

VI. CLINICAL APPLICATIONS

A. Diseases of the aorta

1. **Aortic aneurysm.** MRI can clearly visualize both the aortic vessel wall and lumen. It is a reliable method for the identification, characterization, and follow-up of thoracic and abdominal aortic aneurysms, with accuracy comparable to that of CT. A combination of spin-echo sequences for characterization of the vessel wall, gradient echo cine sequences for dynamic imaging of the aorta and aortic valve, and contrast-enhanced magnetic resonance angiography (CE-MRA) for aortic and branch vessel luminography is characteristically used. The aorta may be highly tortuous and should be imaged in multiple planes, with double-oblique measurements performed from true short-axis cuts using reconstructed images.
2. **Aortic dissection.** MRI is a highly sensitive and specific technique for the detection of aortic dissection (sensitivity 98% to 100%, specificity 98% to 100%). Spin echo, B-SSFP, and CE-MRA are used to identify the intimal flap, true and false lumens, and involvement of aortic branch vessels, including the coronary arteries. Administration of contrast is not critical to the examination, so that MRI may be particularly helpful in patients in whom there is concern for significant renal impairment. In addition, potential complications of aortic dissection (e.g., pleural effusion, pericardial tamponade, and aortic regurgitation) are easily evaluated. However, the longer study acquisition time with MRI compared with CT and its unsuitability for imaging of unstable patients limit its application in

the acute setting. However, as a safe, noninvasive, relatively fast technique and without use of ionizing radiation, MRI is well suited for follow-up of both surgically and medically treated aortic dissections, in particular for young patients.

3. **Intramural hematoma and penetrating aortic ulcer.** Intramural hematoma can be considered as the *forme fruste* of aortic dissection with the spontaneous rupture of one of the vasa vasorum within the media of the aortic wall. It occurs in up to 30% of all acute aortic syndromes and appears as a smooth crescentic to circumferential area of thickened aortic wall without evidence of blood flow in the false channel on either B-SSFP or spin-echo sequences. Because of the short T1-relaxation time of fresh blood, differentiation from the adjacent mediastinal fat may be difficult. Intramural blood can be best detected on fat-saturated T1-weighted gradient echo or black-blood techniques. Furthermore, on spin-echo (“black-blood”) imaging, the intramural hematoma may be isointense (acute) or hyperintense (subacute) relative to skeletal muscle. Penetrating aortic ulcers appear as deep ulcerations of an aortic atheroma that extend through the intima to disrupt the underlying media and cause bulging of the outer aortic contour. They commonly appear at the isthmus beyond the left subclavian artery and in the distal descending thoracic aorta near the diaphragm. If acute, there may be evidence of intramural bleeding in the rim adjacent to the ulcer.
 4. **Atherosclerotic disease.** MRI can clearly show irregular thickening of the aorta in atherosclerotic disease. CE-MRA has good accuracy for detecting significant peripheral stenoses and occlusions. Recent research has focused on the ability of MRI to accurately identify and characterize atherosclerotic plaques in the aorta and carotid arteries, as well as the development of novel contrast agents that target atherosclerotic plaques.
 5. **Trauma to the aorta.** MRI may detect chronic or missed aortic tears, usually related to a previous motor vehicle accident. Tears are usually found in the area of the ligamentum arteriosum and are characterized by a localized saccular aneurysm, with or without an associated periaortic hematoma.
 6. **Aortitis.** In patients with inflammatory disorders affecting the aorta such as Takayasu’s disease (which tends to also involve the arch branch vessels) or giant cell arteritis, MRI can accurately detect diffuse wall thickening of the thoracic and abdominal aorta (specially after gadolinium administration in T1-weighted images) as well as stenosis and occlusion of the aortic branch vessels (CE-MRA sequences). Special imaging sequences using T2-weighting and short-tau inversion recovery for fat suppression, one can also assess for (peri)vessel edema and wall thickening/inflammation, respectively.
 7. **Aortic stents and stent grafts.** Aortic stents and stent grafts can be safely imaged using MRI; however, both cine sequences (gradient echo and B-SSFP) are prone to ferromagnetic artifacts. Spin-echo imaging can be used successfully to evaluate stent graft morphology. Artifacts may limit assessment for graft leaks using CE-MRA.
- B. Assessment of ventricular function and coronary artery disease (CAD)**
1. **Assessment of global ventricular function.** CMRI is now the gold standard for the assessment of ventricular mass, volumes, and systolic function. A significant advantage of CMR is its reproducibility and accuracy compared with 2D planar or projection techniques that depend on geometric assumptions in order to define mass and volume determinations. As a result, small changes in myocardial mass and/or volume can be detected over time or as a result of therapy. A typical approach is to perform a short-axis stack of B-SSFP cine sequences through the left and right ventricles. Manual or semi-automated tracing of the endocardial borders at end-diastole and end-systole is later performed off-line, and ventricular volumes and ejection fraction are calculated using Simpson’s method of discs.
 2. **Assessment of regional ventricular function.** As mentioned before, development of multichannel phase-array coils has enabled parallel imaging and significant

improvements in spatial and temporal resolution and scan times. This has led CMRI to become superior to echocardiography for precise assessment of regional wall motion. B-SSFP cine sequences provide excellent blood-myocardial contrast that permits clear definition of the endocardial border. Furthermore, myocardial tagging methods have also improved the assessment of regional myocardial function.

3. **Myocardial ischemia.** CMRI stress testing can detect myocardial ischemia with either wall motion or perfusion analysis. The use of dobutamine stress CMRI for wall motion analysis is more established than stress perfusion imaging with adenosine or dipyridamole. Studies of stress CMRI with dobutamine have revealed good sensitivity (83% to 92%) and specificity (86%) for the detection of significant CAD on a per-patient level. Furthermore, CMR tagging may further improve the accuracy of dobutamine CMR for ischemia detection. Stress perfusion imaging by CMRI appears to have slightly higher accuracy to that of thallium single-photon emission computed tomography (SPECT), with a sensitivity of 91% and specificity of 81% for the detection of significant CAD reported in a recent meta-analysis. The absence of ionizing radiation with MRI is an important consideration, particularly in younger patients. However, it is important to note that to accomplish these multicenter results, a facility capable of performing the stress testing with appropriate physician and staff training is required.
4. **Myocardial infarction (MI) and viability.** T2-weighted spin-echo sequences with fat suppression may show areas of increased signal intensity consistent with tissue edema in the acute or subacute phase of a MI. This field of myocardial edema has been gaining interest as a target for clinical trials in acute coronary syndrome. The concept is that the myocardium at risk would correspond to the edematous minus the scarred area (seen on delayed enhancement). However, this technique has potential imaging artifacts (cardiac/respiratory motion, low signal-to-noise ratio, slow flow, coil intensity profile, etc) which could hinder the reproducibility of results seen in single-center studies. The current state-of-the-art technique for myocardial scar detection remains delayed enhancement imaging with an inversion recovery gradient echo sequence 10 to 30 minutes after injection of a gadolinium contrast agent. This method shows areas of myocardial scarring as bright and normal myocardium as dark and has shown excellent correlation with the location and extent of scar on histopathologic analysis. The superior spatial resolution of CMRI makes it more sensitive for the detection of myocardial scar, and in particular subendocardial scar, than SPECT or positron emission tomography. In addition, detection of areas of microvascular obstruction, despite adequate epicardial vessel reperfusion, can also be identified with CMRI and appear to be associated with worsened outcomes. The transmural extent of scar is associated with myocardial viability. Transmural or near-transmural scar (> 50%) suggests nonviable myocardium, whereas the absence of myocardial scar suggests that functional recovery is very likely post revascularization.
5. **LV thrombus.** CMR is more sensitive than echocardiography for the detection of LV thrombus which is associated with a greater morbidity. Due to its high spatial resolution and tissue characterization capabilities, CMR can be quite advantageous in establishing or ruling out the diagnosis of intracardiac thrombus. The typical signal characteristics would include lack of contrast perfusion on 1st pass of Gadolinium and low-signal intensity on post-contrast delayed imaging with long inversion time (dark filling defect on the endocardial surface of the left ventricle).
- C. **Nonischemic cardiomyopathies** There is increasing recognition of diffuse myocardial fibrosis occurring as a separate entity in a variety of conditions in the absence of ischemia, including hypertensive and diabetic heart disease, hypertrophic cardiomyopathy (HCM), and idiopathic dilated cardiomyopathy (DCM). In these situations, use of standard delayed enhancement CMR may become a problem: due to the often diffuse nature of the fibrotic process, no true normal, nonfibrotic myocardium can be used as a frame of reference.

To overcome this limitation, several new CMR techniques have been developed in trials for the detection of nonischemic myocardial fibrosis. Contrast-enhanced T_1 mapping using a modified Look-Locker inversion recovery sequence is the most promising technique that allows quantification of diffuse, nonischemic myocardial fibrosis with high temporal resolution within a single breath-hold. However, before it can be used for clinical applications, a more standardized histologically validated technique needs to be identified and assessed in clinical studies on various and larger groups of patients and in multicenter settings.

1. **Dilated cardiomyopathy.** CMRI is useful for precise assessment of cardiac morphology and function in patients with DCM. Delayed enhancement imaging typically shows focal or diffuse enhancement in a mid-myocardial distribution, with a predilection for involvement of the lateral LV wall. Delayed enhancement during the acute presentation of DCM has been shown to correlate with areas of active myocarditis. Thus, CMRI may help guide myocardial biopsy and improve its sensitivity. The extent of delayed enhancement tends to improve over time, but patchy areas often remain and may represent areas of ongoing inflammation or fibrosis.
2. **Hypertrophic cardiomyopathy.** MRI is accurate for the evaluation of the pattern and extent of hypertrophy, systolic anterior motion of the mitral valve, resting left ventricular outflow tract (LVOT) obstruction, and secondary mitral valve pathology and regurgitation. Because of the precise anatomic definition provided by CMRI, it is particularly helpful in planning for surgical myectomy or alcohol septal ablation. CMRI can also help identify abnormal chordal or papillary muscle attachments, which may contribute to LVOT obstruction and have been reported in up to 20% of patients with HCM. Delayed enhancement is frequently seen in patients with HCM and corresponds to areas of interstitial fibrosis. It is typically seen in areas of increased wall thickness as well as the right ventricular (RV) insertion points in the interventricular septum. The extent of delayed enhancement in patients with HCM is associated with the presence of risk factors for sudden cardiac death and associated with worse outcomes. However, further research is needed to prospectively validate and establish a role for myocardial fibrosis detection in risk prediction in patients with HCM.
3. **Restrictive cardiomyopathy (RCM).** Infiltration of the myocardium may lead to RCM, which is characterized by normal ventricular size and systolic function, severe diastolic dysfunction, and biatrial enlargement. LV and RV wall thickness may or may not be increased. CMRI can clearly visualize the typical findings of RCM and simultaneously distinguish it from constrictive pericarditis, the main differential diagnosis. In addition, specific causes of RCM may be diagnosed by CMRI. Amyloidosis is associated with thickening of the interatrial septum and atrial free walls, as well as increased LV and RV wall thickness. Furthermore, **delayed enhancement imaging can show a typical pattern of diffuse subendocardial enhancement in patients with cardiac amyloidosis**, albeit a particular characteristic, best seen in the contrast-enhanced T_1 -weighted scout (Look-Locker) sequence, is the “early” nulling of the infiltrated myocardium—almost concomitant with the blood pool. Several findings have been noted in patients with cardiac sarcoidosis, including areas of increased or decreased signal intensity on T_2 -weighted images and patchy areas of delayed hyperenhancement. **Hemochromatosis is characterized by extensive signal loss on T_2 -weighted images, resulting from iron deposition in the myocardium.** Measurement of the T_2 relaxation time of the myocardium (T_2^* technique) allows more precise detection of iron overload. Furthermore, T_2^* technique is also prognostically important in patients with thalassemia major, identifying patients at high risk for heart failure and arrhythmia more so than serum ferritin and liver iron.
4. **Arrhythmogenic right ventricular dysplasia (ARVD).** CMRI is the primary imaging test for patients with suspected ARVD, although nonimaging criteria are also required to confirm the diagnosis. Although CMRI can identify typical features

of ARVD including RV wall thinning, fibrofatty replacement, and focal RV wall aneurysms, according to the recent revised Task Force criteria (Marcus et al, Circulation 2010) presence of RV dilation, global RV dysfunction, and/or regional hypokinesia are more important findings. Fibrofatty replacement of the RV myocardium on CMRI is no longer a diagnostic criterion requiring histopathology confirmation.

The CMRI examination for ARVD is different than that for other cardiomyopathies. Axial and short-axis stacks of high-resolution T1-weighted spin-echo images are acquired through the right ventricle for anatomic definition of the RV and LV myocardium. The spin-echo pulse sequences may be repeated with fat saturation prepulses to facilitate detection of fatty infiltration of the RV free wall. B-SSFP cines are performed in the same axial and short-axis imaging planes for identification of RV wall motion abnormalities. Finally, delayed enhancement imaging is performed for identification of myocardial fibrosis. ARVD must be differentiated from right ventricular outflow tract (RVOT) tachycardia, which is associated with less dramatic findings on CMRI, including focal wall thinning and regional hypokinesia above the level of the crista terminalis in the right ventricle and in the RVOT.

- D. **Diseases of the pericardium.** Normal pericardium appears on MRI as a thin (≤ 2 mm) curvilinear line situated between the epicardial and pericardial fat. The normal pericardium is of low intensity on both T1- and T2-weighted imaging sequences.
 1. **Pericardial effusions** are typically of low intensity on T1-weighted spin-echo images and of high intensity on gradient echo images. The exception is hemorrhagic effusion, which is of high intensity on T1-weighted spin-echo images and of low intensity on gradient echo images.
 2. **Pericarditis and constriction.** MRI can readily define the presence and extent of pericardial thickening (≥ 4 mm), which may be present in acute pericarditis as well as constrictive pericarditis. In **inflammatory pericarditis**, the pericardium may have increased signal intensity on delayed enhancement imaging. CMRI is now the imaging technique of choice in the diagnosis and management of **constrictive pericarditis**. Typical features include **pericardial thickening and tethering associated with conical or tubular deformity of the ventricles**. Secondary changes include atrial enlargement, systemic and pulmonary vein dilation, hepatomegaly, ascites, and pleural effusions. Cine sequences can demonstrate features of constrictive physiology, including diastolic septal bounce and abrupt limitation of late diastolic filling of the ventricles, which is distinguishable from the more generally delayed diastolic filling patterns seen with restrictive cardiomyopathies. Furthermore, real-time cine sequences with free breathing are also important to demonstrate the interventricular dependence with exaggerated septal shift toward the left ventricle during inspiration. MRI is of limited value compared with CT in the evaluation of calcification of the pericardium because of its inability to reliably distinguish between fibrous tissue and calcification.
 3. **Congenital absence of the pericardium**, which may be complete or partial and often left sided, can be demonstrated on CMRI and is typically associated with a leftward orientation and “teardrop” appearance of the heart. Insinuation of lung tissue between the aorta and pulmonary artery and between the inferior surface of the heart and left hemidiaphragm is also characteristically seen.
 4. **Pericardial cysts.** These are benign developmental lesions formed when a portion of the pericardium is pinched off during embryogenesis. Pericardial cysts are classically seen at the right cardiophrenic angle. They typically contain fluid and are well marginated. Spin-echo images demonstrate round or ovoid lesions that are often contiguous with the normal pericardium. Simple cysts demonstrate low signal intensity on T1-weighted and high signal intensity on T2-weighted images. Hemorrhagic or proteinaceous filled cysts show high signal intensity on T1-weighted images.
- E. **Congenital heart disease.** CMRI is now an essential tool in the management and follow-up of patients with congenital heart disease. Scans can be performed safely and

reliably from infancy through adulthood. CMRI provides excellent anatomic definition of simple and complex heart defects and precise, noninvasive quantification of cardiac function and shunts. Because of the complex morphology and physiology in a given patient, MRI examinations are tailored to the individual, with frequent adjustments made during the examination. Consequently, the supervising radiologist or cardiologist should have a thorough understanding of congenital heart disease and be ready to assist at the scanner during the test. Common applications of CMRI in adult congenital heart disease include noninvasive quantification of intracardiac shunts; evaluation of pulmonary regurgitation severity, ventricular volumes and function, and pulmonary artery branch vessel stenosis in patients post tetralogy of Fallot repair; identification of RVOT or branch pulmonary artery obstruction in patients who are post arterial switch for dextro transposition of the great arteries (D-TGA); evaluation of baffle stenosis or leak and RV dysfunction in patients post Mustard or Senning procedure for D-TGA; and assessment for dysfunction of the systemic ventricle in patients with congenitally corrected or levo transposition of the great arteries (L-TGA).

- F. Valvular heart disease.** Although echocardiography remains the primary imaging modality for the diagnosis and management of valvular heart disease, CMRI may provide additional important information in select cases. Particular strengths of CMRI in the evaluation of valve dysfunction include an often clearer visualization of valve morphology, valve planimetry, precise quantification of regurgitant volumes, accurate and reproducible measurement of ventricular volumes and function, and assessment of associated abnormalities (e.g., bicuspid aortic valve and ascending aortic dilation).
- G. Cardiac masses.** CMRI plays a major role in the evaluation of cardiac and pericardiac masses, because in addition to providing excellent anatomic detail, it also has the ability to perform tissue characterization. Thrombus is the most common intracardiac mass. Fresh thrombus has higher signal intensity than myocardium on T1-weighted images. Older thrombi may have increased signal intensity on T1-weighted and decreased signal intensity on T2-weighted images. Thrombi usually have low signal intensity on delayed enhancement imaging and do not demonstrate delayed enhancement even with long inversion time. Myxomas are the most common intracardiac tumor and in addition to a variegated and irregular appearance typically have higher signal intensity than myocardium on T2-weighted spin-echo imaging. Lipomas have a distinctive short T1 and, therefore, high signal intensity on T1-weighted images. Fat saturation sequences that null lipomatous tissue confirm the diagnosis. Fibromas are an uncommon cardiac tumor and are typically seen within the ventricular myocardium in pediatric or young adult patients. They have decreased signal intensity relative to myocardium on T2-weighted images and show rim enhancement on delayed hyperenhancement imaging.

Primary malignant tumors of the heart are rare. Imaging findings suggestive of a malignant cardiac tumor include a right atrial location, invasiveness without respect to the anatomical borders (ie: involvement of > 1 cardiac chamber, extension into the mediastinum or great vessels), associated hemorrhagic pericardial effusion and moderate or greater contrast perfusion/uptake and subsequent heterogeneous delayed-enhancement of the cardiac mass. The most common is angiosarcoma followed by rhabdomyosarcoma. Angiosarcomas are most commonly seen in the right side of the heart and have a heterogeneous appearance with hyperintense areas on T1-weighted images. Delayed hyperenhancement shows heterogeneous enhancement, most marked in the periphery of the tumor. Metastatic disease of the heart is more common and typically involves the myocardium or pericardium. It is not always possible to differentiate benign from malignant cardiac tumors. Features of malignant tumors are local invasion, pericardial involvement, and increased signal intensity relative to myocardium after injection of gadolinium suggestive of increased vascularity. One limitation of CMRI is its reduced sensitivity for the detection of calcification in cardiac masses.

- H. Pulmonary veins.** With the growth of percutaneous RF ablation procedures for atrial fibrillation, imaging of the pulmonary veins is being increasingly performed.

CMRI with spin and gradient echo sequences complemented by CE-MRA is effective in assessing pulmonary vein anatomy and stenoses before and after the procedure.

VII. FUTURE APPLICATIONS

A. Coronary artery assessment. Coronary imaging with CMRI is usually performed with two-dimensional (2D) or 3D gradient echo sequences, with either fat saturation or T2 prepulses to enhance the signal difference between the coronary lumen and the surrounding myocardium, as well as decrease the venous signal. Three-dimensional acquisition with navigator-corrected (free-breathing) data set has higher signal-to-noise ratio when compared with 2D sequences and has now become the established approach to contrast-enhanced MR coronary angiography.

Although CMRI can be used reliably for the detection of coronary artery anomalies, it has not yet fulfilled its early promise for noninvasive imaging of coronary atherosclerotic disease, especially when applied to the broader patient population. The coronary arteries provide significant challenges to imaging by MRI because of cardiac and respiratory motion, their small size and tortuosity, normal cyclic variations in coronary flow, and competing signal from neighboring blood pools. Nevertheless, it can be valuable in patients with a low to intermediate pretest likelihood of CAD (< 20%) where the negative predictive value is similar to CT (> 95%), reliably ruling out CAD. These patients, who are often younger, predominantly female, and require more than one scan over their lifetime, would highly benefit from a radiation-free imaging study.

B. Molecular imaging. MRI shows significant promise for the selective imaging of target tissue or cells using novel molecular contrast agents. Magnetically labeled mesenchymal stem cells have been successfully tracked by MRI in a pig model of stem cell therapy for myocardial injury. Supermagnetic nanoparticles have also been used to detect atherosclerotic plaque in both animal and human studies. Similar to what has been seen in nuclear cardiology, this is a fast growing field with several lines of research.

C. Interventional CMRI. The use of MRI in interventional procedures is appealing because it does not entail exposure to ionizing radiation. MRI has been used successfully to guide a variety of interventional procedures including balloon angioplasty and interatrial septal puncture in animals. In addition, the first human MRI-guided stenting of the iliac arteries has been reported in a study of 13 patients.

ACKNOWLEDGMENTS: *The author thanks Dr. Ronan Curtin for his contributions to earlier edition of this chapter.*

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RECOMMENDED WEB SITES

- <http://www.mrisafety.com>
<http://www.scmr.org>

CHAPTER

52

Parag R. Patel
Milind Desai

Cardiovascular Computed Tomography

- I. INTRODUCTION.** Cardiovascular computed tomography (CT) has continued to rapidly evolve over the past decade, gaining new and expanded indications for noninvasive assessment of the heart, great vessels, and peripheral vasculature. Technological improvements, including increasing numbers of detectors, improved temporal and spatial resolution, and advanced postprocessing, have broadened the clinical utility of this imaging modality. Advanced multidetector computed tomography (MDCT) scanners and new scanning protocols have significantly reduced radiation and contrast dosages. Numerous considerations are involved in the proper selection of cardiovascular CT protocols, and skilled operators are required to plan and interpret these examinations.

II. BASICS OF CARDIAC CT

A. CT physics. In CT, images are created by rotating an x-ray source emitting a fan-shaped beam of x-rays, which then pass through the body. Some x-rays are absorbed or scattered, but others are transmitted and subsequently sensed by detectors located directly opposite the x-ray source. In MDCT, the x-ray tube and detectors are mounted on a gantry that rotates rapidly around the patient as he or she passes through the scanner. As in traditional x-ray radiography, different structures **attenuate** the x-ray beam to differing extents depending on their atomic composition and density, as well as the energy of the incident photons. The data collected by the detectors then go through a complex set of mathematical reconstruction algorithms that create a set of axial images through the technique of **backprojection**. Each voxel in the resulting axial image is ascribed a specific attenuation value, which is expressed in **Hounsfield units (H.U.)**. Using a reference of 0 H.U. for water, -1000 H.U. for air, and +1000 H.U. for bony cortex, different points are assigned their respective attenuation values. This information is then converted into a grayscale image that can be manipulated by the interpreting physician.

B. Technical challenges for cardiac imaging

1. The fast cyclical motion of the heart requires high **temporal resolution** to avoid blurring or degradation of images due to cardiac motion artifact. In cardiac CT, image acquisition is referenced, or **gated**, to the cardiac cycle. Although data can be acquired throughout the cardiac cycle, most image data sets are reconstructed during periods of minimal cardiac motion, typically a brief 100- to 300-millisecond interval in late diastole (60% to 75% of the R-R interval).
2. High **spatial resolution** is required to image relatively small vessels such as the coronary arteries. Current MDCT scanners (64-slice) provide a spatial resolution of 0.4 mm compared with approximately 0.2 mm for invasive angiography, the gold standard.
3. Respiratory motion artifact can be minimized by having the patient hold his/her breath during image acquisition. Most clinically available scanners can cover the entire heart in 10 to 12 seconds, whereas the newest 256-slice MDCT scanners can cover this area in just one or two heartbeats.
4. Rapid improvements in CT technology and protocoling have outpaced research in the field. Many studies investigating the diagnostic and prognostic yield of information gained from cardiac CT are not based on the newest MDCT scanners—but rather on single-beam/detector systems. Further investigation involving randomized controlled studies has been limited by the ethical issue raised by radiation exposure, although this has also been significantly reduced by innovative scanning approaches.

C. Current CT hardware

1. **MDCT** involves using an x-ray tube mounted opposite multiple detector rows on a gantry, which is then rotated around the patient at a rapid rate (220 to 400 ms/rotation). The patient is moved at either a fixed or variable speed, or **pitch**, through the scanner. An increasing number of detectors allows for an increased z-axis (cranial-caudal) coverage, permitting faster scans with improved image quality due to less cardiac and respiratory motion artifact. Temporal resolution is improved by faster gantry rotation, the use of **two x-ray tubes** and detector arrays mounted at 90° angles to each other (dual-source MDCT), and special reconstruction techniques. Dual-source/dual-energy scanners provide substantial improvements by utilizing dual-source MDCT technology as well as dual-energy sources to improve temporal resolution and decrease scatter. The fastest scanners provide a temporal resolution of 83 to 105 milliseconds. Spatial resolution is largely determined by detector architecture (typically 0.4 mm isotropic resolution), although thicker slices (1 to 5 mm) can be acquired to reduce radiation dose according to the study indication. MDCT can be used for both

cardiac and noncardiac studies, and it is now the most widely used type of CT hardware for cardiac imaging.

2. **Electron beam computed tomography (EBCT)**, although rarely used today, was specifically developed for cardiac imaging. It involves the use of a rapidly oscillating electron beam reflected onto a stationary tungsten target. Because there is no mechanical motion within the gantry, EBCT is capable of very high temporal resolution (50 to 100 milliseconds). EBCT was used primarily for the quantitative detection of coronary artery calcification (CAC).

D. Image acquisition techniques

1. **Acquisition modes.** Most current MDCT scanners use spiral retrospectively gated acquisition techniques for cardiac imaging, as this mode provides the greatest flexibility in image selection during different phases of the cardiac cycle and the ability to edit the image data set for artifacts due to ectopic beats. Recently introduced software has made the older prospectively gated axial acquisition mode possible for cardiac imaging in selected patients, and this has resulted in a 60% to 70% reduction in radiation dose.
 - a. **Sequential (axial, “step-and-shoot”) mode.** Single transaxial slices are sequentially acquired while the patient table is incrementally advanced between successive rotations of the gantry.
 - b. **Spiral (helical) mode.** Data are continuously acquired during constant rotation of the gantry with simultaneous, constant (z-axis) movement of the patient through the scanner. As the tube does not perform a complete rotation in any plane, x-ray data are interpolated from a series of sequential frames to create a single tomographic image.
2. **Electrocardiogram (ECG) gating**
 - a. **Prospective triggering.** The trigger signal is derived from the patient's ECG based on a prospective estimation of the R-R interval. The scan is usually triggered to begin at a defined point after the R wave, usually allowing image acquisition to occur during diastole. Prospective ECG triggering is one of the most dose-efficient ways of cardiac scanning, as only the very minimum scan data needed for image reconstruction are acquired. Limitations of prospective triggering (or “gating”) include the fact that the acquired data set will be of a limited portion (or phase) of the cardiac cycle only, limiting the opportunity for evaluating image data sets from other cardiac phases. In addition, prospective triggering depends greatly on the regularity of the patient's heart rate and can result in serious misregistration artifact in the setting of arrhythmia.
 - b. **Retrospective gating.** Unlike prospective triggering, retrospective ECG gating collects data during the entire cardiac cycle. Once the scan is complete, data from specific periods of the cardiac cycle are used for image reconstruction by retrospective referencing to the ECG signal. This approach allows reconstructions to be made from multiple segments of the cardiac cycle and allows some assessment of cardiac function via four-dimensional reconstruction. However, retrospective gating requires higher radiation dose exposure, although this can be somewhat mitigated by **dose modulation** (see subsequent text).
3. **Other imaging considerations**
 - a. **Segmented reconstruction** refers to image acquisition algorithms that use scan data from more than one cardiac cycle for image reconstruction. This can reduce the effective temporal resolution of the scan at the cost of a slight increase in radiation dose.
 - b. **Dose (or tube current) modulation.** MDCT scanners may operate with fluctuating tube currents that increase radiation dose during portions of diastole (when diagnostic images are most likely to be obtained) and reduce it

during systole. Dose modulation typically reduces effective radiation dose by approximately 33%, and it is most effective at lower heart rates.

4. **Image reconstruction and interpretation.** Images are most frequently viewed from axial and double oblique planes, in which the three-dimensional data set is manipulated by the interpreting physician so that multiple planes can be viewed to assess cardiac morphology and coronary anatomy. Additional postprocessing techniques can be performed to provide further diagnostic information or, more frequently, to present to the referring physician.

- a. **Multiplanar reformation** involves creating straight or curved image planes by cutting orthogonally or obliquely through the three-dimensional acquisition. This aids in evaluating complex three-dimensional structures, such as the coronary arteries.
 - b. **Maximal-intensity projections** are created by compressing a predetermined volume of image data into a two-dimensional projection of the brightest voxels. This is similar in principle to the two-dimensional images created by typical invasive angiography.
 - c. **Three-dimensional or volume rendering** is an advanced image processing approach that uses semitransparent visualization of the outer contours of volumetric data, giving the appearance of a three-dimensional structure. Although often not as useful for assessing smaller structures, these reconstructions can be very helpful for understanding complex spatial relationships between major intrathoracic structures.
 - d. **Four-dimensional or cine imaging** from spiral retrospectively gated images generates cine images of the CT data for evaluating cardiac and valvular function.
- E. **Contrast-enhanced imaging.** Administration of iodinated contrast media increases the attenuation of the blood pool, improving vessel delineation and tissue characterization. When using contrast, image acquisition must be timed such that images are acquired when the blood pool saturation in the target structure is maximal. Various techniques exist to time the arrival of the contrast bolus in the arterial tree and initiate imaging. The specific risks of contrast media are discussed in Section IV.

III. INDICATIONS. The role of cardiac CT in evaluating patients with cardiovascular disease continues to evolve. Generally accepted indications for cardiac CT are listed in Table 52.1 and are discussed in the context of specific clinical situations in Section VI. The following is a brief listing of the more common indications for MDCT.

- A. **Evaluation of chest pain** is performed in patients with low to intermediate pretest probability of disease and persistent chest pain after an equivocal stress test.
- B. **Suspicion of coronary artery anomalies.** Due to high spatial resolution and the ability to create three-dimensional reconstructions of the vasculature, MDCT has very high sensitivity and specificity for coronary anomalies.
- C. **Pulmonary vein evaluation** can be performed often before or after pulmonary vein isolation (PVI) for atrial fibrillation.
- D. **Evaluation of cardiac masses** in conjunction with or when other modalities such as transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), or magnetic resonance imaging (MRI) are unrevealing.
- E. **Evaluation of pericardial disease** in conjunction with or when other modalities such as TTE, TEE, or MRI are unrevealing.
- F. **Assessment of anatomy in complex congenital heart disease.**
- G. **Presurgical evaluation, particularly before redo open heart surgery.** MDCT can aid in describing prior bypass graft location, identifying safe sites for surgical approach.
- H. **Assessing graft patency after prior bypass surgery** is feasible in many cases, although it is sometimes limited by artifacts related to calcium and surgical clips.

TABLE 52.1 Appropriate Indications for Cardiac Computed Tomography

Category	Specific appropriate indications
Suspected CAD with symptoms	Intermediate pretest probability of CAD with uninterpretable ECG or unable to exercise Acute chest pain with intermediate pretest probability of CAD and no ECG changes and negative serial enzymes Evaluation of anomalous coronary artery anatomy Chest pain syndrome with uninterpretable or equivocal stress test (exercise, perfusion, or stress echo)
Evaluation of intra- and extra-cardiac structures	Evaluation of cardiac mass in patients with limited images from TTE, MRI, or TEE
Pericardial disease	Evaluation of pericardial conditions (pericardial mass, constrictive pericarditis, or complications of cardiac surgery) in patients with limited images from TTE, MRI, or TEE
Congenital heart disease	Assessment of complex congenital heart disease including anomalies of coronary circulation, great vessels, and cardiac chambers and valves
Pulmonary vein anatomy	Evaluation of pulmonary vein anatomy prior to invasive radiofrequency ablation for atrial fibrillation
Biventricular pacing	Noninvasive coronary vein mapping prior to placement of biventricular pacemaker
Aortic disease	Evaluation of suspected aortic dissection or thoracic aortic aneurysm
Pulmonary disease	Evaluation of suspected pulmonary embolism
Surgical planning	Noninvasive coronary arterial mapping, including internal mammary artery, prior to repeat cardiac surgical revascularization

CAD, coronary artery disease; ECG, electrocardiogram; MRI, magnetic resonance imaging; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography.

Adapted from the ACCF/ACR/SCCT/SCMR/ASNC/NASCI/SCAI/SIR 2006 appropriateness criteria for cardiac computed tomography and cardiac magnetic resonance imaging. *J Am Coll Cardiol.* 2006;48:1475–1497.

- I. Evaluation of aortic disease.** MDCT is the test of choice for evaluating aortic aneurysm and suspected aortic dissection. It can be useful in the long-term follow-up of patients who have undergone prior aortic surgery or endovascular stenting.
- J. Evaluation of suspected pulmonary embolism (PE).**

IV. CONTRAINDICATIONS. Unlike with cardiac MRI, few absolute contraindications exist for cardiac CT. However, there are important risks associated with radiation and/or contrast exposure that must be weighed against the benefits of the scan. **Relative contraindications** to CT scanning are listed below.

- A. Renal insufficiency.** Given the potential for contrast-induced nephropathy, patients with significant renal insufficiency (i.e., Cr > 1.6 mg/dL) should not undergo contrast-enhanced CT unless the information from the scan is critical and the risks/benefits are thoroughly discussed with the patient.

- B. Contrast (iodine) allergy.** Patients with allergic reactions to contrast should be pretreated with diphenhydramine and steroids before contrast administration. A prior anaphylactic response to contrast is generally felt to be an absolute contraindication to intravenous iodinated contrast administration in many institutions.
- C. Recent intravenous iodinated contrast administration.** Patients who have received an intravenous dose of iodinated contrast should avoid contrast-enhanced CT scanning for 24 hours to reduce the risk of contrast-induced nephropathy. For younger patients with normal renal function without risk factors for contrast-induced nephropathy, contrast doses of up to 150 to 200 mL per 24 hours are generally well tolerated.
- D. Hyperthyroidism.** Iodinated contrast is contraindicated in the setting of uncontrolled hyperthyroidism due to possible precipitation of thyrotoxicosis.
- E. Atrial fibrillation,** or any irregular heart rhythm, is a contraindication to coronary CT angiography due to image degradation from suboptimal ECG gating.
- F. Inability to breath-hold for at least 10 seconds.** Image quality will be significantly reduced due to respiratory motion artifact, if the patient cannot comply with breath-hold instructions.

V. SAFETY

- A. Radiation exposure** is recognized as an important risk of various cardiac imaging modalities, including CT. Radiation doses of cardiac CT scans vary greatly depending on the scan parameter settings, scan range (cranial–caudal length of the scan), gender (women receive more radiation due to breast tissue), and patient's body habitus (obesity increases exposure).
 - 1. Estimates of radiation dose from MDCT** have varied widely in the literature. **Effective dose** is an estimate of the dose to patients during an ionizing radiation procedure and is expressed in **millisieverts (mSv)**. For reference, the estimated dose from a chest x-ray is 0.04 to 0.10 mSv, and the average annual background radiation in the United States is 3 to 3.6 mSv. Invasive diagnostic coronary angiography provides effective doses of 2.1 to 4 mSv. In comparison, coronary CT angiography studies have reported doses ranging from 3.6 mSv to as high as 18 mSv, depending on the scan parameters, with most estimates ranging from roughly 4 to 11 mSv. Table 52.2 lists radiation dose ranges for the most commonly used cardiac imaging modalities.
 - 2. Feasibility of low-dose coronary CT angiography.** With the use of prospective ECG triggering, axial imaging modes, dose reduction, and software adaptations, recent studies have reported the feasibility of coronary CT angiography with comparable image quality and substantially reduced radiation doses (i.e., 1.1 to 3.0 mSv). This remains an area of active investigation.
- B. Contrast-Induced Nephropathy.** Iodinated contrast media can cause renal ischemia by reducing renal blood flow or increasing oxygen demand and may also have a direct toxic effect on tubular epithelial cells. If a contrast-enhanced CT study is necessary in patients with significant renal insufficiency, prophylactic measures should be taken to reduce the risk of renal damage. Most cardiac CT studies require between 80 and 100 cc of contrast dye.
 - 1. Risk factors**
 - (a) Preexisting renal insufficiency
 - (b) Diabetes mellitus
 - (c) Volume of contrast media
 - 2. Prophylactic measures** include saline hydration, use of low-osmolar agents, and sodium bicarbonate infusion, although the data for each of these measures remain somewhat controversial. The use of *N*-acetylcysteine has been shown to have no effect in slowing the progression of contrast-induced nephropathy.

TABLE 52.2 Estimated Radiation Exposure from Cardiac Imaging Procedures

Diagnostic procedure	Typical effective dose (mSv)	Equivalent period of natural background radiation
Natural background radiation	3–4 (range 1.5–7.5)	1 y
Chest x-ray (PA and lateral)	0.04	6 d
Transatlantic flight	0.03	5 d
Lung ventilation (Kr 81m)	0.1	2–4 wk
Lung perfusion study (Tc 99m)	1	4–6 mo
Calcium scoring	0.8–2	3–6 mo
CT head	2	8 mo
Cardiac catheterization (diagnostic)	3–4	1 y
64-Slice MDCT (with dose modulation)	8–12	2–3 y
Myocardial perfusion (TI 201)	15–18	4–5 y
CT abdomen/pelvis	10–20	3–6 y
Cardiac PET	14–20	4–6 y

PA, posterolateral; MDCT, multi-detector computed tomography; mSv, millisievert; CT, computed tomography; PET, positron emission tomography; R, Roentgen units.

VI. CLINICAL APPLICATIONS

A. Coronary calcium scoring uses the observation that coronary calcium is a surrogate marker for coronary atherosclerotic plaque. Studies have shown that the complete absence of coronary artery calcium makes the presence of significant coronary luminal obstruction highly unlikely and indicates a very low risk of future coronary events. Men tend to have higher calcium scores, and individuals of either gender with renal insufficiency or diabetes tend to have higher coronary calcium scores.

1. Either noncontrast EBCT or MDCT can be used (typically with 3.0 mm slice thickness). Contrast is not necessary because calcium is readily identified secondary to its very high x-ray attenuation coefficient (high H.U. score).
2. The **Agatston CAC volume score** is the most frequently used scoring system. It is derived by measuring the area of each calcified coronary lesion and multiplying it by a coefficient of 1 to 4, depending on the maximum CT attenuation within that lesion. It is important to realize the reproducibility of the Agatston score before applying the recommended guidelines for cut-off points. Importantly, the variability in the score has very little meaning at the very high and very low scores. Inter-reader variability can be as high as 3%.
 - a. The **CAC score** can be classified into five groups: (1) zero, no coronary calcification; (2) 100, mild coronary calcification; (3) > 100 to 399, moderate calcification; (4) > 400 to 999, severe calcification; and (5) > 1000, extensive calcification.
 - b. The CAC score is age specific and gender specific. Therefore, there has to be a comparison of the individual data with a “normal” cohort in order to produce meaningful data, usually presented as the percentile distribution. In

general, CAC develops 10 to 15 years later in life in women than in men. Similarly, CAC is generally five to seven times lower at any given age in women than in men.

- c. In a typical cohort of coronary artery disease (CAD) patients, the median CAC score is 975 for men and 370 for women. In comparison with a CAC score of 0, the presence of any CAC is associated with a fourfold risk of coronary events over 3 to 5 years.
 - d. In patients at intermediate clinical risk for coronary events (e.g., by Framingham score), the CAC score can help reclassify patients to a higher or lower risk group. For instance, a CAC score of 0 confirms low risk of events. Conversely, a CAC score of > 400 is observed with a significant cardiac event rate ($> 2\%$ per year) in patients who appear to be of intermediate risk per Framingham score.
 - e. Because statins have no documented effect on CAC progression, there is no value in repeating CAC in persons with a score of > 100 or the 75th percentile.
3. However, not every atherosclerotic plaque is calcified, and even the detection of a large amount of calcium does not imply the presence of significant stenoses. Therefore, it adds only incrementally to traditional risk assessment and should not be used in isolation. The test is most useful in intermediate-risk populations, in which a high or low score may reclassify individuals to a higher or lower risk group, respectively. Unselected screening is not recommended.
- B. Coronary CT angiography** has been shown to be an accurate noninvasive modality for visualizing the coronary arteries, with high sensitivity (85% to 95%) and specificity (95% to 98%) compared with invasive angiography as the gold standard.
1. Coronary CT angiography for evaluating CAD is most useful in low- to intermediate-risk patients with angina or anginal equivalent. The **negative predictive value** of coronary CT angiography is uniformly high in studies, approaching 95% to 100%; in other words, coronary CT angiography is an excellent modality for ruling out coronary disease.
 2. Patients who are generally poor candidates for coronary CT angiography include those who are likely to have heavily calcified coronary arteries (older than 75 years, end-stage renal disease, and Paget's disease), atrial fibrillation/flutter, frequent ventricular ectopic beats, or uncontrolled tachycardia. Quantification of stenosis severity is often impossible in densely calcified arteries, whereas image quality is significantly degraded in patients with arrhythmias or tachycardia. The negative predictive value dropped to 83% in one study, where patients with Agatston's CAC score of < 600 were included.
 3. Known severe CAD is generally a contraindication to coronary CT angiography. However, cardiac CT has been shown to have high sensitivity and specificity for the assessment of bypass graft patency in patients with previous coronary artery bypass grafting (see subsequent text).
 4. **Stent patency.** Patients with prior coronary artery stents are generally poor candidates for CAC and CT angiography, although selected patients with proximal left anterior descending or left main stents may be successfully imaged. Current CT technology does not allow for the accurate quantification of in-stent stenosis severity, due to blooming artifact from the metallic body of the stent.
 5. When assessing the coronaries, **noncalcified plaque** appears as a low to intermediate attenuation irregularity in the vessel wall. **Calcified plaques** are bright, high-attenuation lesions in the vessel wall and may be associated with positive remodeling of the vessel. Densely calcified plaques are often associated with **calcium blooming artifact**, which can lead to overestimation of luminal stenosis severity.

6. The accuracy of coronary CT angiography is highest in the larger proximal to medium vessels, which are more likely to benefit from an invasive management strategy. Coronary stenoses are generally categorized as mild (< 50% diameter stenosis), moderate (50% to 70% diameter stenosis), or severe (> 70% diameter stenosis).

C. Bypass graft imaging

1. **Graft location.** MDCT can accurately characterize the origin, course, and touchdown of prior bypass grafts using intermediate slice thickness (e.g., 1.5 mm). This can be important for surgical planning (see details in subsequent text of this chapter).
2. **Graft patency.** Using a protocol similar to that used for coronary artery assessment (> 1 mm slice thickness), patency of both arterial and venous bypass grafts can be assessed. Studies have suggested that the sensitivity and specificity of MDCT for detecting stenosis or occlusion of bypass grafts, when compared with invasive angiography, are 97% and 97%, respectively. Occasionally, artifacts related to metallic clips can interfere with assessment of the distal anastomosis of an arterial graft (internal mammary or radial artery graft).

D. Coronary artery anomalies. Due to the three-dimensional data acquisition, MDCT is an excellent modality for assessing patients with known or suspected coronary artery anomalies. MDCT can accurately assess the origin and course of anomalous coronaries and can describe the relationship of the coronary artery to neighboring structures. Although MRI can also be used to assess anomalous coronaries without the need for radiation exposure, the spatial resolution, ease of data acquisition, and reliable image quality of MDCT make it a reasonable first choice. Intramyocardial **bridging** can also be detected with high sensitivity, although the clinical significance of this relatively common finding is uncertain.

E. Cardiac morphology/function. Contrast-enhanced MDCT can provide high-resolution morphologic images of the cardiac chambers as well as accurate assessment of right and left ventricular systolic function. However, other imaging modalities such as echocardiography or MRI, which do not require radiation exposure, are generally preferred initially for assessing cardiac morphology.

1. Patients with prior **myocardial infarction** can have fibrous replacement of myocardium with or without calcification, ventricular wall thinning, aneurysm formation, and cavitory thrombus. This is a rare indication for cardiac CT; rather, it is studied with delayed enhancement MRI.
2. **Ventricular dysplasia** is characterized by fibrous and/or fatty replacement of myocardium, ventricular wall thinning and/or focal aneurysm formation, and ventricular cavity dilation with regional or global wall motion abnormalities.
3. **Mass.** CT provides somewhat less information about tissue type than cardiac MRI, although the attenuation of a mass (in H.U.) can be helpful. For instance, lipomas have low CT numbers, cysts have water density (i.e., 0 to 10 H.U.), and thrombi have low to intermediate CT numbers. Atrial myxoma can be visualized easily in the left atrium, although right atrial masses may be difficult to visualize due to contrast mixing at the junction of the right atrium and inferior vena cava (IVC).

F. Pericardial diseases. The pericardium appears as a thin line (1 to 2 mm) surrounding the heart, usually visible with a small amount of adjacent pericardial fat. The pericardium normally enhances with contrast administration; hyperenhancement of the pericardium in the appropriate clinical setting is characteristic of pericarditis.

1. By CT, **congenital absence of the pericardium** is easily diagnosed.
2. Findings of pericardial **constriction** on CT include irregular pericardial thickening and calcification, conical or tubular compression of one or both ventricles,

- enlargement of one or both atria, dilation of the IVC, and a characteristic diastolic bounce of the interventricular septum.
3. Pericardial effusions can be reliably detected by CT, and a small amount of fluid is normal even in healthy subjects. Pericardial tamponade is better evaluated by echocardiography, however, due to its ability to provide hemodynamic information.
 4. A pericardial **cyst** will appear as a well-circumscribed paracardiac mass with characteristic water attenuation (H.U. = 0), usually in the right costophrenic angle.
 5. Both primary **neoplasms** and, more commonly, metastatic neoplasms can be visualized in the pericardium.
- G. Congenital heart disease.** MDCT may be used in selected patients in whom echocardiography is nondiagnostic or inadequate and MRI is not available. The ability to evaluate cardiovascular anatomy in multiple planes is often helpful for delineating cardiac morphology in congenital heart disease, particularly with regard to the relationship of the great vessels, pulmonary veins, and coronary arteries. Specific situations in which MDCT is helpful include “hard-to-find” adult shunt detection (sinus venosus atrial septal defect and patent ductus arteriosus); visualization of pulmonary arteries in cyanotic congenital heart disease; precise definition of aortic anatomy in Marfan’s syndrome or coarctation; and definition of partial or total anomalous pulmonary venous drainage. Additionally, CT can be useful for follow-up imaging in patients with congenital heart disease who have had prior pacemaker or ICD implantation, such as L-transposition of the great arteries.
- H. Diseases of the aorta** constitute a common and important indication for CT examinations. Contrast-enhanced MDCT is nearly 100% sensitive and specific for evaluating acute aortic syndromes. ECG gating is critically important for studies of the aortic root and ascending aorta, given the propensity for motion artifacts to appear similar to dissection flaps on nongated studies.
1. **Acute aortic dissection** (see Chapter 26) is characterized on CT by visualization of a dissection flap (i.e., separation of the intima from the media) that forms true and false lumens. The CT study can characterize the origin and extent of the dissection, classify it as type A or B, assess for concomitant aneurysmal aortic dilation, and identify branch vessel involvement.
 2. **Aortic intramural hematomas** are believed to be caused by spontaneous hemorrhage of the vasa vasorum of the medial layer. They appear as crescent-shaped areas of increased attenuation with eccentric aortic wall thickening. Unlike dissections, hematomas do not spiral around the aorta.
 3. **Aortic aneurysm** is a permanent dilation of 150% of the normal aortic caliber (usually > 5 cm in the thoracic aorta and > 3 cm in the abdominal aorta). Given the often tortuous course of a dilated aorta, it is important that these measurements be made in the true short axis of the aorta, as oblique cuts can result in erroneous overestimation of the aortic diameter. Quantitative measurements of an aortic aneurysm can be made for planning endovascular repair with a **stent graft**.
 4. **Penetrating atherosclerotic ulcer.** These tend to be focal lesions of the descending thoracic aorta that appear as contrast-filled irregular outpouchings of the aortic wall.
- I. Evaluation of pulmonary veins.** In the context of electrophysiology interventions such as PVI, preprocedural MDCT can be used to define pulmonary venous anatomy and identify supernumerary veins, and postprocedural MDCT can be used to evaluate for pulmonary vein stenosis. Additionally, in the setting of congenital heart disease, CT can be used to identify anomalous pulmonary venous return.

- J. Evaluation of PE.** MDCT is highly accurate in detecting PE, which appears as a filling defect in the pulmonary arteries. This modality is most sensitive for proximal (main through segmental branches) thrombi, and small, distal emboli may be missed.
- K. Valvular heart disease.** Visualization of the valve leaflets, particularly the aortic valve, is feasible with newer generation scanners due to their improved temporal resolution. Nonenhanced MDCT is also useful for assessing mechanical valve leaflet motion in cases of suspected thrombosis or infection.
- L. Surgical planning.** The utility of MDCT in surgical planning before cardiothoracic surgery, particularly for reoperations, is increasingly recognized. Preoperative scans can evaluate the proximity of mediastinal structures to the sternum (i.e., aorta, right ventricle, and bypass grafts) and the degree of aortic calcification (i.e., to guide cannulation sites) and concomitantly provide information about cardiac morphology (e.g., presence of a ventricular aneurysm).
- M. Peripheral arteries.** MDCT can also be used to evaluate peripheral arteries, including the carotid, renal, visceral, and lower extremity vessels. Indeed, imaging these vessels is generally more straightforward than coronary imaging, due to their large caliber and minimal motion. CT can be used for planning and follow-up of vascular disease in these peripheral vascular beds. Given the larger caliber of these vessels, assessment of stent patency is often quite feasible.

ACKNOWLEDGMENTS: *The author thanks Drs. Deepu Nair, Paul Schoenhagen, Richard D. White, Sandra S. Halliburton, and Stacie A. Kuzmiak for their contributions to earlier editions of this chapter.*

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RELEVANT GUIDELINES AND APPROPRIATENESS CRITERIA

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SECTION

X

Electrophysiologic Procedures

EDITOR

Thomas D. Callahan

Electrophysiologic Studies

I. INTRODUCTION. Electrophysiologic studies (EPSs) are a specialized form of cardiac catheterization that help identify, characterize, and manage cardiac arrhythmias. Over the past 25 to 30 years, EPSs have advanced our knowledge of mechanisms of cardiac arrhythmias and revolutionized the way these arrhythmias are managed. The studies should be performed by trained clinicians with the help of skilled laboratory personnel in appropriately equipped laboratories. A joint task force of the American College of Cardiology and the American Heart Association in collaboration with Heart Rhythm Society has published guidelines outlining the accepted indications and the training required for personnel performing EPSs.

II. INDICATIONS. The indications for EPSs can be divided into three broad categories: bradyarrhythmias, tachyarrhythmias, and syncope.

- A. Bradyarrhythmias** can be caused by sinus node dysfunction, atrioventricular (AV) nodal disease, or infranodal conduction system disease. EPSs for bradyarrhythmias are rarely necessary because the decision to implant a pacemaker depends primarily on correlation between symptoms and documented bradycardia or demonstration of severe bradycardia or prolonged pauses. EPSs should complement the clinical evaluation, conventional 12-lead electrocardiogram (ECG), and Holter or event monitor. EPSs can be of value in identifying disorders associated with adverse outcome, such as severe infranodal conduction system disease.
- B.** More often, EPSs may suggest bradycardia as the underlying disorder among patients with **syncope** of unknown cause. Thus, patients with syncope of uncertain cause may benefit from EPSs.
- C.** EPSs are of tremendous value in evaluating **tachyarrhythmias**. They are generally more successful in reproducing re-entrant cardiac rhythms than those caused by triggered activity or enhanced automaticity. Among patients with re-entrant tachyarrhythmias, EPSs are useful in documenting the presence of the anatomic or physiologic substrate responsible for the arrhythmia, defining electrical mechanism of the arrhythmia and its associated hemodynamic response, as well as guiding therapy. The response of the tachyarrhythmia during an EPS to various drugs or pacing maneuvers may also be helpful in further defining the underlying substrate and prognosis.

III. EQUIPMENT AND SETTING

- A.** The most important element in the performance of a safe and useful EPS is the presence of **well-trained personnel**. The presence of at least one trained physician and well-trained laboratory support personnel, including a nurse, as well as engineering assistance to maintain and repair the laboratory equipment is necessary. Personnel involved should be familiar with basic electrophysiologic and electropharmacologic principles, the indications for EPSs, and the various diagnostic and therapeutic modalities that can be used in the laboratory.

- B. It is important that the laboratory be equipped with appropriate high-quality **radio-graphic equipment**.
- C. Appropriate selection of **tools** is a very important aspect of the performance of a safe and cost-effective EPS. The minimum instrumentation required for a complete study is a stimulator, an amplifier, display monitors, reliable recording devices, and an external defibrillator.
 - 1. The **stimulator** must be capable of burst pacing, delivery of at least three or four extra stimuli, synchronization to appropriate electric events during intrinsic or paced rhythms, and an adjustable current output. An appropriate unit should have a constant current source and minimal current leakage. It should also be relatively easy to manipulate.
 - 2. The **junction box** connects the electrode catheters to the recording apparatus and the stimulator.
 - 3. **Recording** is best achieved on solid media (e.g., CD or other optical media).
 - 4. The presence of at least two functioning **external defibrillators** is extremely important, particularly during studies in which ventricular arrhythmias may be induced.
 - 5. The presence of a cardiac surgical team in the same institution is not mandatory for routine EPS or simple radiofrequency (RF) ablation procedures. However, for more complex RF ablation procedures where full heparinization is used and where cardiac perforation is a potential complication, the presence of a cardiac surgical team allows for prompt, definitive therapy when surgical intervention is required.
- D. **Intracardiac signals** are recorded using various **electrode catheters**.
 - 1. The most common catheters used are **quadripolar woven Dacron polyester or polyurethane**. The distal poles of these catheters can be used for pacing.
 - 2. For general purpose sensing and pacing in the atrium or ventricle, a **nondeflectable catheter** is usually sufficient. Deflectable catheters facilitate mapping and ablation by allowing more precise movement.
 - 3. Interelectrode distance varies from 2 to 10 mm. Smaller interelectrode distance is useful for precise mapping and timing.
 - 4. For most EPSs, **bipolar recording** is used. However, in some situations, especially during mapping of tachyarrhythmias, unipolar recording can be of value in localizing the earliest sites of activity.

IV. TECHNIQUES AND PROCEDURES

A. Preprocedure preparation

- 1. Before the patient is taken to the EPS laboratory, a **discussion** of the indications and proposed procedure is conducted with the patient, and informed consent is obtained.
- 2. For most indications, EPS is an **elective** procedure. The patient's condition should be clinically **stable** at the time of the study. EPSs on patients who are unstable, including those with active, recent, or untreated coronary disease or those with clinical heart failure, carry much higher risk for complications.
- 3. **Electrolytes, serum digoxin level, and bleeding measurements** are checked and verified as being within the acceptable range.
- 4. Conscious sedation using a mild **sedative** (e.g., a benzodiazepine) and analgesic is administered.
- 5. The patient is attached to continuous ECG and blood pressure **monitoring** devices.

B. Access and catheter placement

- 1. The usual approach to inserting electrode catheters is through the **femoral veins under local anesthesia**, unless there is a clear contraindication to this approach, such as the presence of deep venous thrombosis or an inferior vena cava filter. In

the latter situations or when a coronary sinus (CS) catheter is difficult to insert, a superior vein approach may be used. We routinely utilize vascular ultrasound to directly visualize the femoral venipuncture, particularly when patients are on anticoagulation. This real-time visualization clarifies anatomic variants and enables us to avoid inadvertent arterial needlesticks and multiple passes that can lead to bleeding complications. Sheaths are then introduced into the vein over guidewires via the modified Seldinger technique.

2. Up to three **introducers** are placed in each femoral vein depending on the planned procedure. For patients with **left-sided bypass tracks or left ventricular (LV) tachycardia**, access to the left side of the heart is necessary. This can be achieved through the retrograde transaortic approach via an arterial access or by transseptal puncture via a femoral vein access. Systemic heparin is used for all left-sided procedures, and activated clotting time is monitored during the procedure to achieve adequate levels of anticoagulation.
3. **For a complete EPS, three catheters are needed.**
 - a. One catheter is placed in the **high right atrium**, preferably in the appendage or against the high lateral wall. Another is placed in the **right ventricular (RV) apex**, and the third is placed across the **tricuspid valve** to obtain a His electrogram.
 - b. To obtain a **His electrogram**, the electrode catheter is advanced into the right ventricle across the anterior septal portion of the tricuspid valve. Under gentle clockwise torque, the catheter is then slowly withdrawn to straddle the tricuspid valve. A high-frequency sharp deflection that precedes ventricular activation and follows septal atrial activation represents a **His or proximal right bundle potential**. If the catheter is drawn further, this sharp signal occurs slightly earlier. A satisfactory position of the His catheter is achieved when an atrial signal is recorded followed by the His potential and, finally, the ventricular potential is recorded via the same pair of electrodes.
4. In **supraventricular tachycardia (SVT)** studies, when a left-sided accessory pathway or left atrial origin is suspected, an octapolar or decapolar catheter may be placed in the CS rather than in the high right atrium. This more stable catheter position allows mapping of the left AV groove along the mitral annulus. Although the CS is easily entered from the superior venous approach, successful catheterization is expected in most attempts through the femoral approach as well. The catheter is placed in the CS with the proximal electrodes just inside the CS ostium.

C. Baseline assessment

1. When all the catheters are in place, a baseline ECG (generally leads I, aVF, V₁, and V₆) and intracardiac electrograms are obtained (Fig. 53.1).
2. In general, **cycle lengths** rather than beats per minute are measured. The following measurements are made at baseline: sinus cycle length and PR, QRS, QT, AH, and HV intervals. To convert an arrhythmia's rate from cycle length to beats per minute, divide 60,000 by the cycle length to obtain the arrhythmia rate in beats per minute.
 - a. The **AH interval** is measured from the onset of the local A deflection to the H deflection on the His electrogram.
 - b. The **HV interval** is measured from the H deflection on the His electrogram to the earliest ventricular activity in any lead (surface or intracardiac).
3. When measurements are made during pacing, it is important to **measure from the resulting deflection** rather than from the pacing artifact to avoid errors caused by latency (delay between the pacing artifact and activation at the recording site).
4. All measurements are recorded in **milliseconds**. Interpretation of baseline intervals is shown in Figure 53.2.

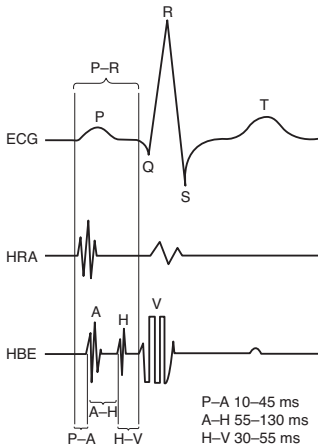


FIGURE 53.1 Normal baseline intervals. Typically, up to four surface ECGs (I, aVF, V₁, and V₆) are displayed along with atrial (CS), His (HBE), and ventricular (RVA) electrograms. CS7–8 refers to the proximal bipolar CS electrogram. Fast sweep speeds are used, ranging from 100 to 400 mm/s. On the time scale, each large division is 100 milliseconds, and each minor division is 10 milliseconds. In addition to intervals, pattern of atrial and ventricular activation should be evaluated. If the CS catheter is placed correctly (see text), the earliest A in sinus rhythm is seen on the HRA electrogram (not shown), then on the His electrogram, and progressively later along the CS electrograms. In the absence of bundle branch block or left-sided accessory pathway, the earliest ventricular activity is seen on right-sided electrograms (His and RV electrograms). (Adapted from *Dorland's Illustrated Medical Dictionary*.) CS, coronary sinus; ECG, electrocardiogram; HBE, His bundle electrogram; HRA, high right atrium; RVA, right ventricular apex.

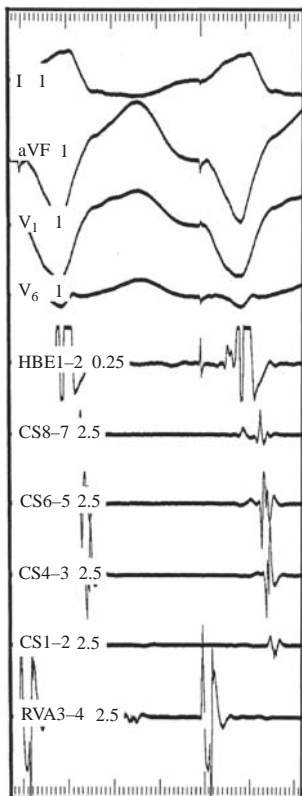


FIGURE 53.2 Programmed ventricular stimulation using double extra stimuli in a patient with AV node re-entry tachycardia. Note that the earliest retrograde atrial activity is seen on the His electrogram. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

D. Programmed stimulation

1. After baseline measurements are made, programmed stimulation is performed. The protocol used depends on the indication for the study and varies among institutions. During programmed stimulation, the **hemodynamic response** of the patient to pacing and induced tachycardia is closely monitored. For example, rapid ventricular pacing in patients with structural heart disease may result in transient hypotension. If this occurs, pacing should be limited in duration and adequate time between pacing drive trains should be allowed for hemodynamic recovery.
2. **Pacing stimuli** are usually delivered at 1 or 2 millisecond pulse width and at twice diastolic pacing thresholds. This is important during ventricular stimulation because pacing at higher outputs increases the risk of inducing nonclinical rhythms. There are two main types of programmed stimulation: burst pacing and the extra stimulus technique.
 - a. **Burst pacing** involves continuous pacing at rates faster than the patient's intrinsic rate.
 - b. In the **extra stimulus technique**, premature beats are introduced either during intrinsic rhythm (sensed extra stimuli) or after a paced drive train (paced extra stimuli). Extra stimulus techniques are useful in evaluating refractory periods of the AV node, atrial tissue, ventricular tissue, and accessory pathways. It is possible to evaluate infranodal conduction system refractory periods with atrial or ventricular stimulation. Extra stimulus techniques are also useful in inducing, terminating, and identifying re-entrant arrhythmias.
 - (1) In the **sensed extra stimulus** technique, a single extra stimulus (S_2) is introduced initially with a coupling just below the intrinsic rate. The coupling interval is reduced progressively by 10 to 20 milliseconds until the premature stimulus no longer captures. A pause of 2 to 5 seconds is allowed between stimulation sequences. Multiple extra stimuli (S_3 , S_4) can be added if necessary and the sequence repeated.
 - (2) In the **paced extra stimulus** technique, a drive train of 6 to 10 beats at a fixed cycle length is followed by the premature beat. The drive train cycle length (S_1S_1) usually ranges from 350 to 800 milliseconds (most frequently 400 to 600 milliseconds) but depends on the resting heart rate. When this technique is used, testing at two drive train cycle lengths is recommended. The premature stimulus (S_2) is introduced with a coupling interval just below the S_1S_1 . The coupling interval of the premature stimulus is decreased progressively by 10 to 20 milliseconds until it no longer captures. The longest coupling interval (S_1S_2) that does not capture the myocardium is the absolute refractory period. S_3 and S_4 are added if necessary. This protocol can be varied depending on the indication and operator preference.
3. **Continuous monitoring** and recording of external and intracardiac electrograms is maintained throughout programmed stimulation. When a particular event such as a tachycardia occurs, stimulation is stopped and the event evaluated. The operator should be ready to respond to the event appropriately, depending on the effect that the event has on the patient. For example, induction of a sustained tachycardia may result in severe hypotension, angina, or loss of consciousness. In such circumstances, expeditious termination of the tachycardia is indicated through overdrive pacing or cardioversion. The operator should also be ready to perform pacing or other maneuvers to further assess the mechanisms and re-entrant circuit of the induced tachycardia.

V. ATRIAL STIMULATION

- A. An atrial study is an integral part of EPSs. The only time an atrial study is not performed is in the presence of persistent atrial fibrillation.

1. **Burst atrial pacing** at incremental rates causes slowing of AV nodal conduction (a process known as decremental conduction) and can induce tachycardia, including AV node re-entry tachycardia and AV re-entrant tachycardia. Other forms of tachycardia unrelated to AV nodal conduction can also be induced, such as atrial flutter, atrial fibrillation, atrial tachycardia, and certain forms of idiopathic ventricular tachycardia.
 2. Burst pacing is performed by means of **continuous pacing** (e.g., 10 to 20 stimuli) at a fixed cycle length starting at 100 milliseconds below the baseline cycle length. Repeat burst pacing is performed at progressively shorter cycle lengths until 1:1 conduction through the AV node is no longer maintained. The shortest cycle length showing consistent 1:1 conduction through the AV node is recorded. This is related to the **effective refractory period** of the AV node, which is the longest A_1 – A_2 interval that fails to be conducted to the His bundle. Another interval that can be measured is the **functional refractory period** of the AV node: it is defined as the shortest output interval from the AV node to the His bundle, given any input signal.
 3. If a patient is believed to have **atrial flutter** or **atrial tachycardia**, repeat burst pacing at even shorter cycle lengths is performed until 1:1 atrial capture is no longer maintained.
- B. Another form of atrial stimulation that is performed is paced extra stimulus.**
1. The **effect of atrial premature beats** on the AH interval is assessed. The normal response of the AH interval is to progressively prolong with shorter A_1 – A_2 coupling. This is a direct demonstration of the normal decremental conduction properties of the AV node.
 2. At a critical A_1 – A_2 , the AV node fails to conduct, and on the His electrogram an atrial signal is seen without a His or ventricular deflection. This indicates that a **block has occurred in the AV node**. It is important to continue stimulation until the atrial refractory period is reached because a gap phenomenon may occasionally exist as a result of dual AV nodal pathways.
 3. The **gap phenomenon** is demonstrated by apparent achievement of the AV nodal refractory period followed by resumption of conduction at shorter A_1 – A_2 coupling intervals. It reflects functional differences in conduction velocity or refractoriness in several regions of the AV junction.
 4. If **narrow complex tachycardia** is induced, it is evaluated with regard to type, mechanism, response to maneuvers, and method of termination (see Section IX.B.3).
- C. Sinus node evaluation.** For patients who may have underlying sinus node dysfunction, sinus node tests are sometimes performed.
1. **Sinus node recovery time (SNRT)** is evaluated through burst pacing at various cycle lengths in the atrium for 30 to 60 seconds, followed by abrupt termination of pacing. SNRT is the escape interval between the last paced atrial beat and the first atrial recovery beat. A **corrected sinus node recovery time (CSNRT)** is calculated by means of subtracting the baseline sinus cycle length from SNRT. A normal value for CSNRT is < 550 milliseconds. SNRT is used to evaluate the automaticity mechanism of the sinus node.
 2. **Sinoatrial conduction time (SACT)** is a combined measure of conduction in the atrial tissue that includes the area of the sinus node and sinus node automaticity. The assumptions are first that the conduction times into and out of the sinus node are equal, second that the pacing train does not alter the automaticity of the sinus node, and third that the pacemaking site does not change after premature stimulation. The SACT is measured with one of two methods.
 - a. In the **Strauss method**, a sensed premature atrial beat is used to reset the sinus node, and the return cycle length after the premature beat is measured. The basic cycle length is subtracted from the return cycle length, leaving out

the time necessary to penetrate and leave the sinus nodal tissue. SACT is one-half this interval.

- b. In the **method proposed by Narula**, the same measurements are obtained after pacing for eight beats at a rate slightly faster than the sinus rate. The upper range of SACT is 100 to 120 milliseconds.

The sensitivity of each individual (SACT and SNRT) test in diagnosing sinus node dysfunction is approximately 50% when used alone and 65% when combined. The specificity of the two combined tests is 88%, which gives the test a high positive predictive value. However, because of its low sensitivity, a normal test does not exclude sinus node disease.

VI. VENTRICULAR STIMULATION

- A. Ventricular stimulation is performed in evaluations of suspected SVTs or ventricular tachyarrhythmias. Some SVTs, such as unusual forms of AV nodal re-entry, may be more easily induced with ventricular stimulation. To further characterize the tachycardia, the response of the tachycardia to premature ventricular beats can be assessed.
 1. When ventricular stimulation is performed for the evaluation of ventricular or wide complex tachyarrhythmias, **pacing at two or more sites** maybe necessary. These sites are typically the RV apex and the RV outflow tract.
 2. Before programmed stimulation is begun, pacing thresholds are determined, and the output of the pacing stimulus is set to twice the diastolic capture threshold. Higher outputs or coupling intervals shorter than 200 milliseconds may cause induction of nonclinical arrhythmias.
- B. **Burst pacing in the right ventricle** is one of two techniques used when assessing retrograde ventriculoatrial (VA) conduction in the evaluation of SVT.
 1. The presence of **retrograde atrial activation** is documented, and a sequence or pattern of atrial activation is evaluated.
 2. The **earliest atrial activity** during retrograde conduction via the AV node is typically recorded on the His electrogram (see Fig. 53.2). This indicates that retrograde conduction has proceeded through the AV node fast pathway. **Absence of VA conduction**, with rare exceptions (e.g., the Mahaim type of accessory pathway which only conducts in the antegrade direction), excludes the presence of a bypass track. The **presence of eccentric atrial activation** (late atrial activation on the His electrogram; see Fig. 53.3) suggests the presence of a retrogradely conducting bypass track.
 3. For some patients with no evidence of retrograde VA conduction, infusion of low doses of **isoproterenol** or a small dose of atropine (0.5 mg) restores this property to the AV node.
 4. The **shortest paced cycle length** capable of 1:1 conduction to the atrium is documented.
- C. Premature ventricular stimulation is another technique used to evaluate retrograde conduction properties of the heart.
 1. If **retrograde conduction** is present, the refractory periods of the conducting pathways are determined with the extra stimulus technique.
 2. In patients with **retrograde VA conduction through the AV node**, conduction block of a ventricular premature beat frequently occurs in the His-Purkinje system rather than in the AV node. His-Purkinje conduction block is more likely to occur at long drive trains. Such drive trains therefore are more likely to induce AV re-entry tachycardia (using a bypass track) by facilitating retrograde His-Purkinje block and allowing a retrograde conducted beat through the pathway to propagate antegrade through the AV node.
- D. In patients being evaluated for **ventricular arrhythmias**, programmed stimulation with extra stimuli is the initial technique used. Pacing at two drive train cycle lengths (e.g., 600 and 400 milliseconds) is performed with single, double, and triple extra stimuli. Simultaneous atrial pacing at the same drive train cycle length is sometimes necessary to avoid competition from the intrinsic atrial pacemaker.

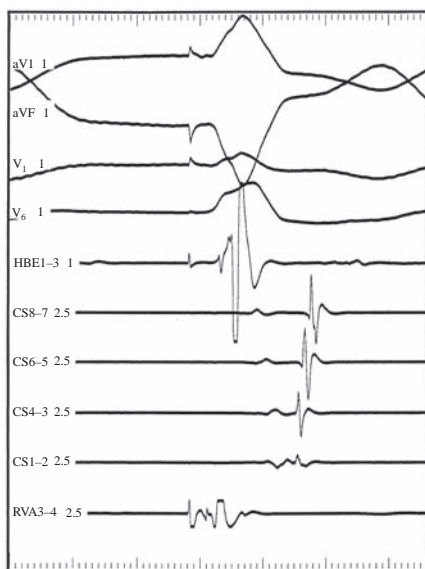


FIGURE 53.3 This is an example of a 17-year-old patient with left lateral manifest pathway. Ventricular stimulation results in retrograde atrial activation, with the earliest A seen in CS1–2 (eccentric atrial activation). CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

- E. Like the A_1A_2 technique described earlier, V_2 is introduced at progressively shorter coupling intervals (V_1V_2) until V_2 no longer captures (ventricular refractory period). Then V_2 is set at a coupling interval longer than the refractory period and V_3 is introduced at progressively shorter coupling intervals until it no longer captures. The use of triple extra stimuli (V_3V_4) is usually reserved for patients being evaluated for ventricular arrhythmias.

A pause of 4 to 5 seconds is allowed after each cycle to assess response and for the patient to recover after ventricular pacing. An increase in the number of extra stimuli increases the sensitivity of the study in reproducing clinical arrhythmias, but at the cost of a lower specificity due to initiation of polymorphic ventricular tachycardia or ventricular fibrillation.

If programmed stimulation with ventricular extra stimuli does not induce ventricular tachycardia in a patient at very high risk, other techniques may be used. One is **burst pacing in the ventricle**. A series of 10 paced ventricular beats are introduced at a constant cycle length. The paced cycle length is then decreased by 50 to 100 milliseconds in successive bursts until reaching within 50 milliseconds of the predicted refractory period of the right ventricle, when the decrements proceed at 10-millisecond intervals until 1:1 capture is no longer maintained. Burst pacing in the atrium can at times induce idiopathic LV tachycardia in susceptible persons.

- F. In some patients, particularly those with underlying dilated cardiomyopathy, **bundle branch re-entry (BBR) tachycardia** (see Fig. 53.4) may be induced.
1. This type of tachycardia usually involves the right bundle branch as the antegrade limb and the left bundle branch as the retrograde limb of the re-entrant circuit. It is usually a rapid and hemodynamically unstable tachycardia.
 2. Because His bundle refractoriness increases after a pause, a short-long-short stimulation sequence can be used to cause retrograde block in the right bundle so that the paced stimulus can conduct retrograde up the left bundle branch and possibly initiate tachycardia if the right bundle branch is no longer refractory for antegrade conduction.

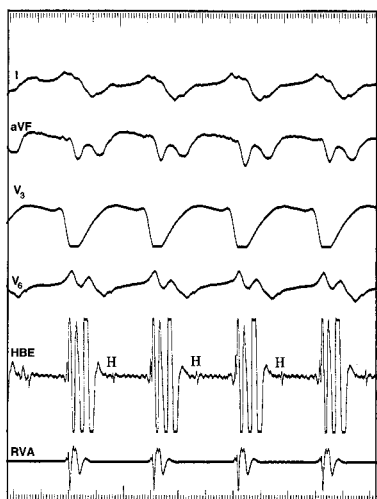


FIGURE 53.4 Bundle branch re-entry tachycardia. This example is from a 52-year-old man with dilated cardiomyopathy who presented with syncope. This ventricular tachycardia exhibits left bundle branch block morphology, and there is an H deflection preceding every V on the His electrogram. To be absolutely certain of this diagnosis (as opposed to myocardial ventricular tachycardia with retrograde His), one has to look for cycle length variation and document that changes in the H–H interval precede changes in the V–V interval. HBE, His bundle electrogram; RVA, right ventricular apex.

3. The sequence most commonly used consists of a 6-beat drive train at 400 milliseconds followed by V_2 coupled at 600 to 700 milliseconds. V_3 is then introduced at a coupling interval 100 milliseconds longer than the refractory period of the ventricle. V_2 – V_3 is progressively decreased until V_3 no longer captures. V_4 can be introduced if necessary.

VII. INDUCTION OF VENTRICULAR FIBRILLATION. Under certain circumstances, the operator may decide that induction of ventricular fibrillation is necessary. This is of value when testing implantable defibrillators for detection of arrhythmias and during assessment of defibrillation thresholds. Ventricular fibrillation can be induced by means of direct application of alternating current or rapid ventricular pacing at high output. The current can be delivered through a catheter electrode or through the **implantable cardioverter-defibrillator (ICD)** lead. Another means of inducing ventricular fibrillation is to deliver a low-energy shock (around 1 J) via the intracardiac leads at the peak of the T wave.

VIII. USE OF CARDIOACTIVE DRUGS DURING EPSs. Cardioactive drugs can be used during EPSs as diagnostic or therapeutic agents. The drugs most commonly used are isoproterenol, procainamide, atropine, and adenosine.

A. Isoproterenol in doses ranging from 0.5 to 5 $\mu\text{g}/\text{kg}/\text{min}$ is used during EPSs to facilitate induction of SVTs and ventricular tachyarrhythmias.

1. For patients with SVTs that are AV node dependent, isoproterenol facilitates conduction through the AV node by means of shortening its refractoriness.
2. It is not absolutely certain how isoproterenol facilitates induction of ventricular tachycardia, but possible mechanisms include enhanced conduction, altered refractoriness, and enhanced automaticity related to delayed afterdepolarization.
3. Isoproterenol is particularly useful in evaluating patients with exercise-induced ventricular tachycardia and patients with the special type of RV outflow tract tachycardia. Isoproterenol is contraindicated in the presence of critical coronary artery disease.
4. Adrenergic stimulation with high doses of isoproterenol (up to 20 $\mu\text{g}/\text{min}$) also effectively induces repetitive rapid discharges from the pulmonary veins that frequently trigger initiation of atrial fibrillation (see Section **IX.B.3**).

- B. Procainamide** is used less frequently during EPSs. Among patients believed to have advanced underlying conduction disease, the response of the infranodal conduction system to procainamide infusion (10 to 15 mg/kg) is assessed during sinus rhythm and with atrial pacing.
1. Considerable prolongation of the HV interval or induction of infranodal block with atrial pacing at cycle lengths longer than 400 milliseconds is considered by many experts to be evidence of His-Purkinje disease. Procainamide can facilitate the induction of atrial and ventricular arrhythmias by means of slowing conduction.
 2. Procainamide is often used to prevent recurrent atrial fibrillation when programmed atrial stimulation is necessary. An example would be a patient with atrial flutter who is being evaluated for ablation and is easily induced into atrial fibrillation during programmed stimulation.
 3. Procainamide was widely used in the past for risk assessment among patients with inducible ventricular tachycardia. Studies have shown that patients with suppressible ventricular tachycardia have better long-term prognosis (lower rate of clinical recurrence and lower mortality) than those with non-suppressible ventricular tachycardia. However, with wider use of ICDs and evidence of their superiority even among persons with suppressible ventricular tachycardia, this application of procainamide may be of historical interest only.
- C. Adenosine**, in doses that produce transient AV block (6 to 18 mg), is used frequently in EPSs of patients with SVTs to define the mechanism of the tachycardia, establish AV node dependence, or document the presence or absence of accessory pathway conduction before and after RF ablation. It may also be used after atrial fibrillation ablation to assess inducibility of atrial fibrillation.

IX. INTERPRETATION OF FINDINGS IN EPSs

- A. Bradyarrhythmia evaluation.** EPSs are *not* indicated when symptomatic bradycardia is documented. Among patients who have a clear indication for implantation of a permanent pacemaker, findings of EPSs are unlikely to alter that decision. However, EPSs are more helpful to patients believed to have underlying **sinus node or conduction system disease and symptoms** but for whom noninvasive monitoring has failed to document a correlation between bradycardia and symptoms. EPSs are also helpful in assessing patients who continue to have symptoms after permanent pacemaker implantation.
1. **Baseline evaluation.** Sinus bradycardia, sinus arrest with junctional or ventricular escape, various degrees of heart block, and intraventricular conduction delay, isolated or in various combinations, may occur among patients with bradycardia and can be further evaluated by examining the intracardiac recordings.
 - a. **Conduction intervals** are measured and evaluated. Disease in the AV node often produces prolongation in the AH interval, whereas disease in the infranodal conduction system produces prolongation in the HV interval.
 - b. A long HV interval is suggestive but not diagnostic of an underlying bradyarrhythmia. It is commonly associated with wide QRS on surface ECG. A long HV interval at rest can be considered an indication for prophylactic pacemaker implantation (class IIa) if it exceeds 100 milliseconds.
 - c. Documentation of intermittent spontaneous infranodal block or infranodal block in response to atrial pacing (see Fig. 53.5) or upon administration of procainamide is an indication for implanting a permanent pacemaker.
 2. **Programmed stimulation**
 - a. After baseline intervals are measured, **SNRT and SACT** are determined. SNRT is used to evaluate automaticity of the sinoatrial node.
 - b. Rapid pacing causes overdrive suppression of the sinus node. Among patients with sinus node dysfunction, recovery time after cessation of pacing is

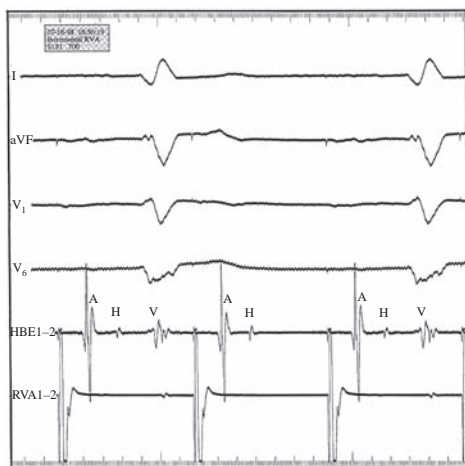


FIGURE 53.5 Intrahisian block in response to slow atrial pacing. This tracing is from a 70-year-old man who presented with syncope. Baseline H–V was 110 milliseconds. As shown in this tracing, burst pacing in the right atrium at cycle length of 700 milliseconds resulted in intermittent intrahisian block (H deflections not followed by V). This patient had a dual-chamber pacemaker implanted. HBE, His bundle electrogram; RVA, right ventricular apex.

prolonged. The situation is similar to sudden termination of atrial fibrillation, which can be followed by a prolonged post-conversion pause.

- c. After cessation of pacing, the **longest SNRT following pacing at varying cycle lengths and secondary pauses** is documented. Secondary pauses are those intervals related to the sinus beats that occur after the first escape beat. CSNRT, which is calculated by means of subtracting baseline cycle length from SNRT, is considered abnormal if it exceeds 550 milliseconds.
- d. **SACT** is used to evaluate conduction velocities in the atrium and in tissues surrounding the sinoatrial node. SACT is performed with the methods described earlier. A normal SACT is between 50 and 125 milliseconds. When both CSNRT and SACT are normal, symptoms are uncommon. The sensitivities of CSNRT (54%) and SACT (51%) combined are higher (64%), and the specificity is approximately 88%. The low sensitivity of these tests limits their value in predicting development of symptoms in asymptomatic patients.
- e. **AV node and infranodal conduction system integrity** is tested with atrial stimulation techniques. Attention is paid to the AH and HV intervals during atrial pacing.
 - (1) The refractory period of the AV node is determined at two cycle lengths. The shortest cycle length with 1:1 AV conduction is also determined.
 - (2) The normal AV nodal response to burst pacing at short cycle lengths is second-degree Mobitz I AV block. HV interval prolongation or intrahisian block is not typically observed. If it occurs at cycle lengths longer than 400 milliseconds, HV interval prolongation suggests significant underlying His-Purkinje disease.
 - (3) Prolongation of the AV nodal refractory period is most frequently caused by high vagal tone or concomitant use of medications. It has no predictive or diagnostic value in evaluating patients believed to have bradycardia. However, a long AV nodal refractory period may mask underlying abnormal His-Purkinje refractoriness, and enhancement of AV nodal conduction with atropine or isoproterenol may be necessary during EPSs.
3. **Carotid sinus massage** is performed in all patients undergoing evaluation of bradycardia or syncope.
 - a. Firm pressure is applied over the carotid artery pulsation, behind the angle of the mandible.

- b. A **positive cardioinhibitory response** is present if pauses of 3 seconds or more occur. A **vasodepressor response** is present if blood pressure decreases by > 50 mm Hg in the absence of marked bradycardia. Mixed responses are common.

B. SVT evaluation. One of the most important elements in the evaluation of tachyarrhythmias is careful analysis of the surface ECG during clinical tachycardia. This can give several clues to the underlying diagnosis and make the EPS more focused. Most SVTs that are induced in the EPS laboratory are re-entrant. They include AV nodal re-entry tachycardia, orthodromic AV re-entry tachycardia, atrial flutter, and re-entrant atrial tachycardia. Automatic tachyarrhythmias are relatively uncommon except in acutely ill patients. They characteristically exhibit a warm-up phenomenon and are difficult to induce with extra stimulus techniques, but may be induced with drugs such as isoproterenol.

1. Baseline evaluation

- a. Resting ECG and intracardiac recordings can provide important information about a possible cause even before any tachycardia is induced. The presence of a short PR interval on the ECG and wide QRS complex with a slurred initial deflection suggests preexcitation.
- b. Absence of preexcitation at rest does not rule out the presence of an accessory pathway. For the diagnosis of SVT, an atrial and a ventricular study have to be performed.
- c. If tachycardia is not induced at the baseline study, programmed stimulation in the atrium and ventricle is repeated with isoproterenol.
- d. Some SVTs, particularly those involving AV re-entry using a bypass tract, can be induced with ventricular stimulation, whereas atrial flutter and, to a lesser extent, atrial tachycardia are rarely induced by means of ventricular stimulation.

2. Programmed stimulation begins with burst pacing in the ventricle to document and characterize VA conduction. Absence of VA conduction practically excludes a concealed bypass tract, and ventricular extra stimulus technique may not need to be performed unless ventricular tachycardia is suspected.

- a. **Earliest retrograde atrial activity** is usually seen on the His electrogram during normal retrograde atrial activation through the AV node. Early retrograde atrial activity on the distal CS electrogram, if the position of the CS catheter is correct, suggests the presence of a left-sided accessory pathway (see Fig. 53.4). Early atrial activity in the proximal CS electrodes suggests a posteroseptal pathway or AV node slow pathway conduction.

(1) Eccentric atrial activation is any atrial activation that does not activate the AV node and the area around the AV node first. This is frequently seen with retrograde ventricular stimulation, when the retrograde impulse finds the AV node refractory. The site of earliest atrial activation is then in the distal CS catheter and not in the proximal area closest to the AV node/His bundle. Evidence of eccentric atrial activation may not be clear during burst pacing when there is fusion of retrograde impulses, arriving through both the AV node and the accessory pathway.

(2) The retrograde 1:1 cycle length should be documented.

(3) Programmed ventricular stimulation is performed with single premature beats at two drive train cycle lengths (e.g., 600 and 400 milliseconds). During programmed stimulation, the following are recorded:

- (a) Retrograde refractory periods
- (b) The pattern and any changes in retrograde atrial activation
- (c) The site of retrograde VA block
- (d) The presence of dual retrograde AV node function

(4) If an accessory pathway is found, its retrograde 1:1 conduction cycle length and refractory period are documented.

b. During atrial stimulation, particular attention is paid to the **AH and HV intervals**.

- (1) Sudden prolongation of A_2H_2 of > 50 milliseconds in response to a decrement of 10 milliseconds in A_1A_2 is called a **jump** (see Fig. 53.6) and has been classically described as a sign of dual AV nodal physiology. **However, more recent reports have demonstrated that the normal AV node has dual pathways even if this “jump” is not demonstrated.** Furthermore, initiation of AV nodal re-entrant tachycardia does not require the presence of such a jump in the AV nodal conduction curve.
- (2) Induction of re-entrant tachycardias generally depends on the occurrence of **unidirectional block and conduction delay**. In the case of AV nodal re-entry, antegrade block in the fast pathway combined with critical delay in the slow pathway allows the impulse to conduct retrograde on the fast pathway and excite the atrium. This first retrograde-conducted atrial depolarization is called an **echo beat** (see Fig. 53.6). If this echo beat succeeds in conducting antegrade down the slow pathway again and retrograde up the fast pathway, sustained AV nodal re-entry occurs.
- (3) **Induction of AV node re-entry** is facilitated by use of shorter drive train cycle lengths and, if necessary, use of more than one extra stimulus or rapid burst atrial pacing. Occasionally, initiation of AV nodal re-entry requires ventricular pacing or premature beats.
- (4) In the presence of an accessory pathway, the site of critical delay is also in the AV node. However, to induce orthodromic AV re-entry tachycardia, antegrade block of an atrial impulse has to occur in the accessory pathway so that it is excitable by the time the same impulse propagates

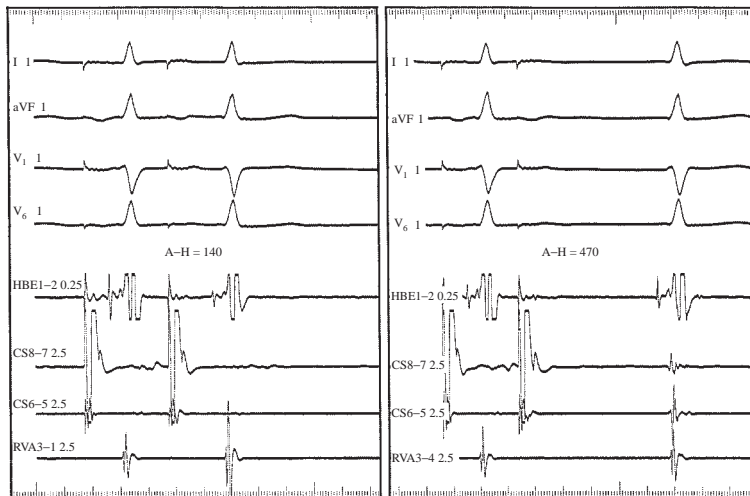


FIGURE 53.6 AV nodal jump and echo. A 10-millisecond decrement in S_1S_2 resulted in marked prolongation of A_2H_2 by > 300 milliseconds. In addition, an echo beat with a short H-A is seen on the CS electrogram, a definite evidence of dual AV node physiology. The atrial premature beat, blocked antegrade in the fast pathway, was conducted with sufficient delay in the slow pathway to encounter a nonrefractory retrograde fast pathway. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.



FIGURE 53.7 Orthodromic AV re-entry tachycardia. In this example from a patient with a manifest right-sided accessory pathway, premature atrial stimulation (S) blocks in the accessory pathway (resulting in a narrow QRS complex), conducts with a longer A–V, and re-excites the atrium. The tachycardia is narrow complex, with an H–A interval of 180 milliseconds. The earliest A is seen on the high right atrial catheter. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

through the AV node and ventricle and arrives to conduct retrogradely through the accessory pathway to the atrium (see Fig. 53.7).

3. Evaluation of induced tachycardia

- a. If a tachycardia is induced, the first assessment is its **hemodynamic consequences**. Hemodynamically unstable tachycardia should be immediately terminated. Only if the tachycardia is hemodynamically stable can further evaluations during tachycardia be conducted.
 - (1) Whether the QRS is narrow or wide, the relation between atrial rate and ventricular rate is noted (AV association or dissociation).
 - (2) Lack of a 1:1 AV relation excludes AV re-entry tachycardia and, for practical purposes, AV nodal re-entry. In rare instances, AV node re-entry tachycardia can exhibit 2:1 AV block.
 - (3) If the atrial rate is faster than the ventricular rate, the diagnosis is **atrial tachycardia or atrial flutter**, depending on the rate and pattern of atrial activation.
 - (4) If the ventricular rate is faster than the atrial rate, the diagnosis is ventricular tachycardia. Alternative causes for AV dissociation include AV nodal re-entry tachycardia with block in the upper common pathway, re-entry tachycardia with a nodofascicular pathway, or a junctional tachycardia with retrograde block.
- b. When a **1:1 AV relation** exists, **further evaluation** is needed. The following observations and techniques are helpful in arriving at the most likely mechanism:
 - (1) **Atrial activation.** The sequence of atrial activation during tachycardia is important in the differential diagnosis of SVT. Accurate placement of catheters is extremely important; catheter misplacement can lead to

inappropriate conclusions or interventions. The **earliest site of atrial activation** is noted. As mentioned above, if earliest atrial activation is in the distal CS, a left atrial tachycardia or AV re-entry using a left-sided accessory pathway is most likely. If an accessory pathway is located in the posterior septum, the earliest A is seen in the proximal CS electrogram. This is also true if the atria are being activated through the slow pathway of the AV node, as in atypical AV nodal re-entry tachycardia.

- (2) The presence of **cycle length variation** during tachycardia helps predict the activation sequence. For example, a change in AA coupling interval before an equal change in HH or VV interval (with changing VA) suggests a diagnosis of atrial tachycardia.
 - (a) In cases of wide complex tachycardia in which there appears to be a 1:1 relation between H and V, HH interval change preceding VV interval change suggests supraventricular or BBR tachycardia.
 - (b) Cycle length variation may also be helpful when there is **slowing of tachycardia with the development of bundle branch block and acceleration with resolution of the block**. This finding is suggestive of AV re-entry using an accessory pathway ipsilateral to the bundle branch block as the retrograde limb. This can be appreciated on the surface ECG. In fact, prolongation in tachycardia cycle length in association with a bundle branch block is caused by prolongation of the VA interval. The activation wavefront must travel down the contralateral bundle and across the intraventricular septum before it reaches the pathway. The change in cycle length is more pronounced with lateral than with septal pathways.
- (3) **HA and VA intervals.** A constant HA or VA relation despite cycle length variation (even in the absence of bundle branch block) is highly suggestive of **AV node re-entry or accessory pathway-mediated tachycardia**. The change in tachycardia cycle length is caused by varying antegrade conduction time through the AV node. The VA time can also be used to differentiate AV nodal re-entry from AV re-entry. A VA interval < 70 milliseconds is rarely seen with AV re-entry and strongly suggests the diagnosis of AV nodal re-entry (see Fig. 53.8). VA times in excess of 70 milliseconds are seen with AV re-entry and atypical AV nodal re-entry (so-called fast-slow AV nodal re-entry).
- (4) **Introduction of premature beats during tachycardia.** Premature ventricular beats are typically introduced during tachycardia at intervals when the His bundle is refractory. Because the normal retrograde path (His-AV node) is refractory, preexciting the atrium with a premature ventricular beat at those intervals is diagnostic of the presence of an accessory pathway capable of retrograde conduction. Consistent termination of tachycardia with such premature beats without retrograde conduction to the atrium is also diagnostic of AV re-entry and excludes atrial tachycardia.
- (5) **Pacing maneuvers during SVT.** During SVT, ventricular pacing maneuvers can be a useful first step in diagnosing the mechanism of tachycardia. Ventricular pacing at a cycle length slightly faster than the tachycardia cycle length is referred to as ventricular overdrive (VOD) pacing. Successful entrainment occurs when VOD resets the tachycardia such that the atrial rate is accelerated to the paced ventricular cycle length and returns to the tachycardia cycle length when ventricular pacing stops and the tachycardia continues. An atrial-atrial-ventricular response upon cessation of VOD, or V-A-A-V response, is diagnostic of atrial tachycardia. A V-A-V response is most consistent with a re-entry tachycardia. The relationship of the post-pacing interval to the tachycardia

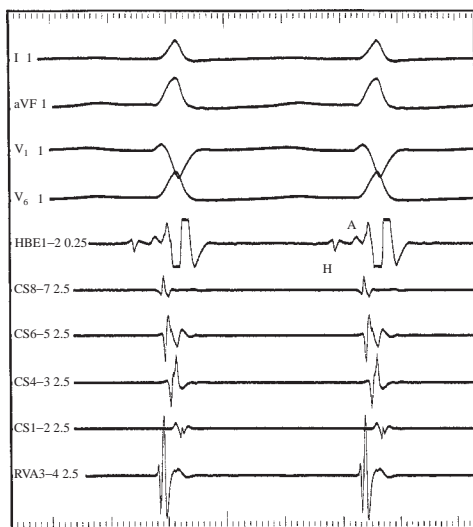


FIGURE 53.8 AV node re-entry tachycardia. Tachycardia is narrow complex and characterized by very short V–A interval and an H–A interval of < 70 milliseconds. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

cycle length can then be helpful in differentiating the type of re-entry tachycardia.

- (6) **Initiation and termination of tachycardia.** To understand the mechanism of tachycardia, it is important to know the mechanism of initiation. For re-entry to occur, block in one limb of the re-entrant circuit and slow conduction in the other limb must take place. It is important to review the stimulation sequences that did not induce tachycardia and compare them with those that did. A sudden jump in the AH interval suggests, but is not diagnostic of, AV nodal re-entry. Orthodromic AV re-entry tachycardia develops during atrial stimulation after antegrade block in the accessory pathway takes place in combination with a critical delay in the AV node. With ventricular stimulation, AV re-entry tachycardia develops after block in the AV node or His-Purkinje system occurs. Termination of the tachycardia simultaneous with AV node block (A with no H) suggests AV node dependence and is helpful in excluding AV node-independent tachycardias (atrial tachycardia and flutter).
4. **Significance of induced tachycardia.** With the exception of atrial fibrillation, induced re-entrant SVTs signify the presence of an established anatomic circuit. Comparison with the clinical arrhythmia is important and, unless significant differences exist, it can safely be assumed that the induced tachycardia is clinically significant. If a wide complex tachycardia with a supraventricular mechanism is induced, the recording is compared with a clinical recording. If the QRS morphology is different from that of the clinical arrhythmia, a search for ventricular arrhythmia may be warranted.
5. **Atrial flutter,** a special type of atrial tachycardia that involves a well-defined anatomic circuit, is amenable to curative catheter ablation techniques.
 - a. In the typical variety of atrial flutter, the waveform travels counterclockwise around the tricuspid annulus. The circuit is bounded anteriorly by the tricuspid annulus and posteriorly by the crista terminalis and its inferior medial continuation as the eustachian ridge. The site of functional block appears to be in the isthmus region, which is the narrow corridor between

the inferior tricuspid annulus and the inferior vena cava. The site of conduction delay or slowing appears to be due to transverse conduction block into the crista, forcing the wavefront to enter the crista at its superior end before propagating down the crista into the isthmus region.

- b. To induce counterclockwise atrial flutter, progressively more rapid (approximately 250 to 200 milliseconds) burst pacing appears to be most successful and is performed anywhere medial to the isthmus. The impulses block in the isthmus and conduct counterclockwise around the tricuspid ring with sufficient delay to sustain atrial flutter. If burst pacing is used lateral to the isthmus, clockwise atrial flutter may be induced. Successful ablation of typical atrial flutter necessitates generation of bidirectional isthmus block by applying a line of RF lesions that spans the posterior isthmus from the tricuspid valve to the inferior vena cava (the cavotricuspid isthmus).
 - c. Less commonly, different types of atrial flutter in which the subeustachian isthmus is not part of the circuit are induced. These atypical flutters have many varieties and locations but share a common re-entrant circuit that revolves around an area of conduction block or delay, usually scar tissue. Treatment involves creating an ablation line from the area of scar to an anatomic barrier or ablating critically narrowed re-entrant paths within a scarred region. The success rates in ablating these atypical forms of atrial flutter are not as high as for isthmus-dependent flutters.
- 6. Atrial fibrillation.** Previous evidence favored multiple re-entrant wavelets as the predominant mechanism responsible for atrial fibrillation. However, it has been recently demonstrated that atrial fibrillation is frequently initiated by rapidly firing foci located predominantly in the pulmonary veins, where sleeves of atrial muscle with abnormal automaticity or perhaps re-entry are present. Our current concept of atrial fibrillation revolves around two factors: a triggering mechanism and a substrate that can maintain atrial fibrillation. Most atria, especially in relatively normal hearts, are quite resistant to initiation of atrial fibrillation. Thus, the concept of focal initiation of atrial fibrillation by rapid bursts of focal atrial tachycardia emerged as a triggering mechanism, making it possible to map and target these sites for catheter ablation. The current understanding is that a vast majority of these triggering sites are near the os of the pulmonary veins in the left atrium.
- a. Ablation of these triggering foci requires left atrial access by transeptal puncture. Following transeptal puncture, a decapolar mapping catheter with a ring configuration called a lasso is used to record electrical activity around the circumference of each pulmonary vein ostium. It displays a far-field atrial signal and a near-field pulmonary vein potential. This is characterized as a very sharp spike following the atrial deflection during sinus rhythm. However, discharges from the vein will invert this activation sequence; the pulmonary vein potential will precede the atrial activation.
 - b. RF ablation is delivered around the roving circular lasso catheter along the antrum of the pulmonary veins to abolish the pulmonary vein potentials. Alternatively, a wide antral circumferential ablation around the pulmonary veins on each side is used to electrically isolate the pulmonary veins from the left atrium. In that manner, abnormal firing would be confined to the veins and no atrial fibrillation would be induced.
 - c. In a minority of cases, atrial fibrillation may be induced by rapid discharges originating from nonpulmonary vein foci, most commonly from the superior vena cava. Circumferential catheter ablation can be performed in the same fashion, aiming at abolition of all venous potentials (electrical isolation).
- C. Evaluation of accessory pathways**
1. The **most common locations** for accessory pathways in decreasing order of frequency are left free wall, posterior region, posteroseptal region, right free wall,

and anteroseptal region. Concealed accessory pathways (no evidence of antegrade conduction) with only retrograde conduction are more common than manifest pathways, which have antegrade conduction manifested by delta waves on the surface ECG, the slurred initial deflection of the QRS that implies preexcitation as described earlier.

- a. **Right-sided accessory pathways** are more likely than left-sided accessory pathways to be associated with **congenital heart disease**. An unusual type of right-sided accessory pathway is the atriofascicular accessory pathways, which originate in the right atrium, traverse the right anterior region of the tricuspid valve annulus, and insert in the region of the right bundle or the right-sided Purkinje network. These accessory pathways have unidirectional antegrade conduction with decremental conduction properties similar to an AV node. These pathways are frequently referred to as Mahaim pathways and typically do not conduct retrogradely.
 - b. **Multiple accessory pathways** are more frequently encountered on the right side and in survivors of sudden death. In these patients, the most common combination is posteroseptal and right free wall pathways.
 - c. Both antidromic and orthodromic AV re-entrant tachycardias require participation of the accessory pathway. In rare instances, antidromic tachycardia can involve one accessory pathway in the antegrade direction and a second pathway in the retrograde direction.
2. Evidence of preexcitation is supported by the presence of **short HV interval** (< 35 milliseconds) **at rest** or with atrial pacing and the appearance of increasing preexcitation either with atrial pacing or with administration of drugs that cause AV nodal conduction slowing, or with autonomic maneuvers. The electrophysiologic properties of the accessory pathway are examined, including its antegrade and retrograde conduction and refractory periods. If tachycardia is induced during atrial or ventricular stimulation, its mechanism is defined according to the techniques discussed earlier. This depends on whether the tachycardia is narrow or wide complex.
 3. **Orthodromic AV re-entry tachycardia** is commonly initiated by a ventricular premature stimulus that blocks in the His-Purkinje system or, rarely, in the AV node, but conducts in a retrograde direction over the accessory pathway. It can also be induced by an atrial premature stimulus (echo beat) that blocks the accessory pathway and conducts slowly over the AV conducting system. Induction is facilitated by the presence of a relatively **long antegrade refractory period of the accessory pathway** or a **long retrograde refractory period of the His-Purkinje system**.
 4. **Antidromic AV re-entry tachycardia** (see Fig. 53.9) can be initiated with burst pacing in the atrium or with a premature atrial stimulus that **blocks in the AV node and conducts over the accessory pathway**. Less often, it can be induced with a premature ventricular stimulus that blocks the accessory pathway in a retrograde manner and conducts over the AV node. Induction of antidromic tachycardia necessitates excellent retrograde conduction over the His-Purkinje system–AV node; it almost always involves a free wall accessory pathway as the antegrade limb and is frequently associated with the presence of multiple accessory pathways.
 5. **Localizing accessory pathways**
 - a. **Surface electrocardiographic localization**
 - (1) **Delta wave vectors**
 - (a) Left lateral: negative I, aVL; positive II, III, aVF; V_1-V_6
 - (b) Left posterior wall: positive I, aVL; negative II, III, aVF; positive V_1-V_3/V_4
 - (c) Posteroseptal: positive I, aVL; negative II, III, aVF; $R/S < 1$ in V_1
 - (d) Right free wall: positive I, aVL, II; negative III; biphasic V_1 and V_2
 - (e) Anteroseptal: positive I, aVL; positive II > III; negative V_1-V_6

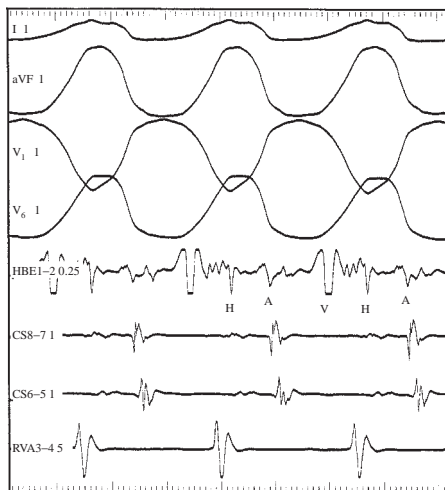


FIGURE 53.9 Antidromic AV re-entry tachycardia. This tachycardia was induced with atrial burst pacing in a young patient with two right-sided manifest accessory pathways. The tachycardia is rapid and wide complex, with the earliest retrograde A seen in HBE1–2, consistent with retrograde activation through the AV node. AV node re-entry with antegrade activation using the accessory pathway (bystander accessory pathway) was excluded by lack of evidence of dual AV node physiology. AV, atrioventricular; CS, coronary sinus; HBE, His bundle electrogram; RVA, right ventricular apex.

(2) P-wave morphology during orthodromic tachycardia

- (a) Left lateral: negative I, aVL; positive III > aVF > II; negative V₅ and V₆
- (b) Posteroseptal: positive aVR, > aVL; negative II, III, aVF
- (c) Right free wall: positive I, aVL, II; negative III; biphasic V₁ and V₂

b. Localization during EPSs

- (1) Pacing from multiple atrial sites: shortest A-delta occurs with pacing close to the atrial insertion site of AP and results in maximal preexcitation.
- (2) Retrograde atrial activation during orthodromic tachycardia and V pacing
 - (a) Atrial activation sequence
 - (i) Left and right free wall: eccentric
 - (ii) Posteroseptal: A_{CSos} earlier than A_{His}
 - (iii) Anteroseptal: A_{CSos} later than A_{His}
 - (b) Atrial activation sequence when a ventricular premature stimulus is delivered during tachycardia at the time when His is refractory
 - (c) The earliest site of atrial activation identifies the site of atrial insertion of an accessory pathway
- (3) Relation of local ventricular electrogram to delta: earliest V correlates with ventricular insertion site. This may be slightly offset or oblique compared with the atrial insertion site.
- (4) Effects of bundle branch block
 - (a) Bundle branch block increasing the VA interval by > 35 milliseconds; ipsilateral free wall accessory pathway
 - (b) With bundle branch block ipsilateral to septal accessory pathways, the increase in VA times is < 25 milliseconds
 - (c) Left anterior fascicular block can increase VA times 15 to 35 milliseconds with left free wall accessory pathway, particularly with an anterolateral left-sided accessory pathway
- (5) Recording of accessory pathway potential: sharp spike 10 to 30 milliseconds before the onset of the delta wave

6. Identifying the presence of multiple accessory pathways

- a. Changing antegrade delta waves during sinus rhythm, atrial pacing, atrial fibrillation, and with antiarrhythmic drugs

- b. Evidence of multiple routes of retrograde atrial activation
 - (1) Changing VA time or activation sequence
 - (2) Failure to prolong VA time with ipsilateral bundle branch block
- c. Orthodromic tachycardia with antegrade fusion
- d. Preexcited tachycardia
 - (1) Antegrade conduction over septal accessory pathway
 - (2) Antidromic tachycardia faster than orthodromic tachycardia
- e. Atypical patterns of preexcitation
- f. Mismatch of site of antegrade preexcitation and retrograde atrial activation during AV re-entry tachycardia

D. Ventricular tachycardia evaluation

1. The most common reason for performing EPS on patients with suspected ventricular arrhythmias is documentation of inducible tachycardia, testing the effect and response to anti-tachycardia pacing and defibrillation, and endocardial mapping to direct attempts at ablation. Recent trials have stratified patients with ischemic or nonischemic cardiomyopathy, congestive heart failure, and reduced LV ejection fraction at higher risk for sudden cardiac death and thus reduced the usefulness of EPS in determining the need for ICD implantation.
2. An **atrial study** is considered for all patients undergoing evaluation of ventricular tachycardia. This serves three main purposes: diagnosis of the underlying advanced conduction system disease, documentation of coexisting SVT, and induction of rare forms of ventricular tachycardia that may be inducible only with atrial pacing.
3. **Programmed ventricular stimulation** is performed as described earlier. If ventricular tachycardia is not induced despite program stimulation from two RV sites (RV apex and outflow tract), repeat stimulation can be performed after isoproterenol infusion. However, isoproterenol should not be given to patients with active ischemic heart disease. It is primarily of value to those with exercise- or catecholamine-dependent ventricular tachycardia. LV stimulation is not necessary because RV stimulation techniques have adequate sensitivity and specificity, and the risk of left heart catheterization is avoided. If no ventricular tachycardia is induced with any of these techniques, the arrhythmia is deemed noninducible.
4. **Techniques for terminating induced ventricular tachycardia.** Pacing terminates as many as 85% of induced ventricular tachycardias in the laboratory. Success is more likely to be achieved with slower tachycardia rates (< 200 beats/min) and in hemodynamically tolerated tachycardias. Other factors predictive of success of pacing include the site of stimulation in relation to the tachycardia zone, ventricular conduction properties, and refractoriness. Pacing can also accelerate tachycardia, an important consideration when anti-tachycardia pacing is being considered.
5. **Techniques for terminating tachycardia with pacing.** One technique entails use of one or more **progressively earlier premature ventricular stimuli**. The other technique uses **burst pacing** to overdrive the tachycardia, but there is a greater risk of accelerating the tachycardia into a hemodynamically unstable arrhythmia. Techniques that can be used if pacing fails include delivery of ultrarapid train stimulation and synchronized direct current cardioversion.
6. There are a variety of **responses to programmed stimulation**. What is important is the correlation between these responses in different populations of patients and future risk of adverse outcome. For example, induction of single or double BBR beats has no bearing on long-term outcome among persons with normal LV function and is not considered an abnormal finding. Induction of sustained monomorphic ventricular tachycardia, particularly among persons with reduced LV ejection fraction, identifies a subset of patients at high risk for sudden death.

a. **Sustained monomorphic ventricular tachycardia**

- (1) Induction of sustained monomorphic ventricular tachycardia is the **most important response** and has the highest predictive value. This is particularly true if the induced tachycardia is similar to the clinical arrhythmia in both rate and structure. Patients with easily induced ventricular tachycardia (e.g., with single premature beats) have worse outcome than those in whom tachycardia is more difficult to induce. It is important to document reproducibility of ventricular tachycardia during programmed stimulation. Slow, sustained tachycardia, particularly in patients with ischemic substrate, is typically more reproducible than more rapid tachycardias and tachycardias in those with nonischemic cardiomyopathies. Sustained tachycardia has clearly worse prognostic implications than nonsustained tachycardia. There is no agreement on what constitutes an abnormal response among patients with nonsustained tachycardia or whether any therapeutic intervention should be pursued for these patients.
- (2) Among patients with ischemic substrate, programmed stimulation induces sustained monomorphic ventricular tachycardia in as many as 95% of patients with a history of clinical sustained ventricular tachycardia, approximately 60% of those with nonsustained ventricular tachycardia, and approximately 50% of patients experiencing sudden cardiac death. Induction of sustained monomorphic ventricular tachycardia in any of the above subsets has very high specificity (> 90%) for spontaneous clinical ventricular tachycardia and sudden death. Testing at two RV sites increases sensitivity without sacrificing specificity.
- (3) Patients with **nonischemic substrate** are more challenging to evaluate because EPSs are less sensitive and specific. Although inducible sustained monomorphic ventricular tachycardia has a worse prognosis than the noninducible type, the positive predictive value of abnormal results of EPS is at best 70%. Patients with negative results of EPS are still at high risk for sudden death, even if they have no prior clinical events. The prognosis may be more favorable if inducible tachycardia is suppressed by drugs, but the risk of future events continues to be high. One can never be reassured about the outcome among patients with nonischemic cardiomyopathy using results of EPS.
- (4) **BBR tachycardia** is a type of ventricular tachycardia with a well-defined macro re-entrant circuit. It occurs most often among patients with dilated cardiomyopathy and is frequently symptomatic.
 - (a) In the **typical pattern**, the impulse travels antegrade down the right bundle branch, across the interventricular septum, and retrograde up the left bundle branch. The tachycardia exhibits a left bundle branch block pattern, with a **His deflection preceding every QRS complex**. In sinus rhythm, the **HV interval is abnormally long**, and during tachycardia it is at least equal and frequently longer than the baseline HV.
 - (b) In rare instances, it is difficult to differentiate BBR tachycardia from an SVT with aberration or from a myocardial ventricular tachycardia with retrograde His deflections.
 - (c) BBR tachycardia is frequently rapid and exhibits AV dissociation. If cycle length variation takes place, it is important to assess the order of changes in the HH and VV intervals. If HH changes take place before VV changes, BBR is likely. A VV change that occurs before HH change and is also associated with a variation in the HV interval suggests myocardial ventricular tachycardia.

- (d) Treatment with **antiarrhythmic agents**, including amiodarone, is not helpful and may lead to stabilization of the re-entrant circuit. BBR tachycardia is curable with RF ablation of the right bundle.
- b. **Polymorphic ventricular tachycardia** frequently occurs with high-output stimulation. It is also more likely to occur with increasing numbers of extra stimuli.
 - (1) **Interpretation** of the induction of polymorphic ventricular tachycardia depends on the clinical situation. For example, inducible polymorphic ventricular tachycardia in a survivor of sudden cardiac death is considered significant. In a patient with ventricular ectopy and normal ventricular function, inducible polymorphic ventricular tachycardia is a nonspecific response.
 - (2) Similar interpretation applies to **induced ventricular fibrillation**. If the patient has never had clinical ventricular tachycardia or ventricular fibrillation and has no underlying heart disease, the induced ventricular fibrillation is considered a nonspecific finding that does not warrant therapy.
- c. Patients with **hypertrophic cardiomyopathy** represent another subset for whom the predictive value of EPS is problematic. Induction of sustained monomorphic ventricular tachycardia, induction of ventricular fibrillation without aggressive stimulation protocols, and induction of ventricular arrhythmias with atrial pacing or as a result of atrial fibrillation are generally considered to be **poor prognostic signs**.
- d. **Summary**. It is important to have a thorough understanding of the underlying clinical problem and anatomic substrate to assess the appropriateness of any EPS finding for an individual patient.
 - (1) Repetitive responses caused by BBR are usually physiologic, whereas intramyocardial repetitive ventricular responses are abnormal. However, neither of these responses should be used to guide therapy.
 - (2) Induced polymorphic ventricular tachycardia and ventricular fibrillation can be considered nonspecific findings or clinically significant depending on the clinical circumstances. However, they should not be used to guide drug therapy in any situation.
 - (3) Induced sustained monomorphic ventricular tachycardia identical to the clinical arrhythmia has the highest sensitivity and specificity and has greater importance in predicting outcome.
 - (4) The importance of nonsustained ventricular tachycardia remains controversial. Noninducibility in patients with nonischemic cardiomyopathy or survivors of sudden cardiac death may not provide prediction as accurate as that for patients with underlying ischemic substrate and documented nonsustained ventricular tachycardia. Therapeutic decisions therefore have been individualized.
 - (5) Guidelines derived from studies including the MADIT trials and the SCD-HeFT have obviated the need for performing EPS before deciding to implant ICDs in particular patient populations.
- 7. **Mapping of ventricular tachycardia**. Mapping of ventricular tachycardia involves identification of the **earliest sites of activation** during tachycardia and detailed outlining of the **tachycardia circuit**. Endocardial mapping has aided in the evaluation of mechanisms of tachycardia. More recently, mapping has been coupled with RF ablation with high rates of success.
 - a. Mapping can be performed with steerable electrode catheters during EPS or can involve introduction of specialized catheters with various configurations designed to compare several simultaneously acquired endocardial electrograms.

- b. For the most part, mapping of ventricular arrhythmias takes place in the left ventricle. However, several types of ventricular tachycardia that originate from the right ventricle, including those from the outflow tract, have been successfully mapped and ablated.
- c. Activation mapping takes place during the tachycardia. The objective is to identify the site of earliest activation. Because this lengthy process has to take place during tachycardia, it must be hemodynamically tolerable. The earliest activation site corresponds to the exit site of the circuit.
- d. Sites of origin of tachycardia in patients with ischemic heart disease are usually found in the periinfarction zone or in the border of an LV aneurysm. To confirm the site, entrainment from that site is performed. Entrainment involves transient overdrive pacing and resetting of the tachycardia without terminating the tachycardia. When entrainment is achieved within the re-entrant circuit inside the slowly conducting scarred regions of the heart, or isthmus, pacing produces QRS morphologic match on all 12 surface ECG leads. The return cycle length of activation at the site of pacing after cessation of pacing equals the tachycardia cycle length (see Fig. 53.10). These two observations imply that depolarization caused by pacing has the same exit from the scar as the tachycardia and that the pacing site is within the circuit.
- e. Pace mapping can be used in evaluations of patients with hemodynamically intolerable tachycardia. Ventricular pacing is performed at various sites at rates that do not cause hemodynamic instability. The site where pacing results in QRS match with clinical tachycardia corresponds to the exit sites of the tachycardia circuit.
- f. **Electroanatomic mapping systems allow the** measurement of tissue voltage, providing accurate delineation of scar tissue and its boundaries. Thus, mapping in sinus rhythm allows for delimitation of the scar and areas of the scar border that are likely sites of tachycardia exit. Pace mapping can be used to identify those sites around the scar that correspond to tachycardia exits. Linear lesions, performed to interrupt these exit sites responsible for re-entrant circuits, can be undertaken, allowing successful ablation of tachycardias that would not be otherwise mapped due to patient intolerance of any sustained tachycardia. Another method of mapping a hemodynamically unstable ventricular tachycardia is to use a mapping system that can acquire the map of the entire endocardium in a single beat. This requires insertion of an “array” catheter into the left ventricle that acquires the electrograms from 64 points on the balloon and calculates the virtual activation on the endocardial surface. Alternatively, an intra-aortic balloon pump or percutaneous LV assist device may be considered to assist with mapping and ablation during prolonged or hemodynamically unstable VT.
- g. Mapping can also be performed intraoperatively when endocardial resection is considered. Although this approach can still be used, it is infrequently recommended, as other approaches described above in combination with implantable defibrillators have yielded good patient survival and excellent success in eliminating problematic ventricular tachycardias.
- h. Some patients including many with nonischemic cardiomyopathy or certain variants such as Chagas disease and hypertrophic cardiomyopathy may require both endocardial and epicardial approaches to VT mapping and ablation. Percutaneous access into the epicardial space is obtained with a subxiphoid approach under fluoroscopic guidance and small injections of contrast until the parietal pericardium is penetrated. In patients with dense pericardial adhesions that may limit catheter movement, an intraoperative subxiphoid incision or open sternotomy may be considered to allow for greater exposure and access.

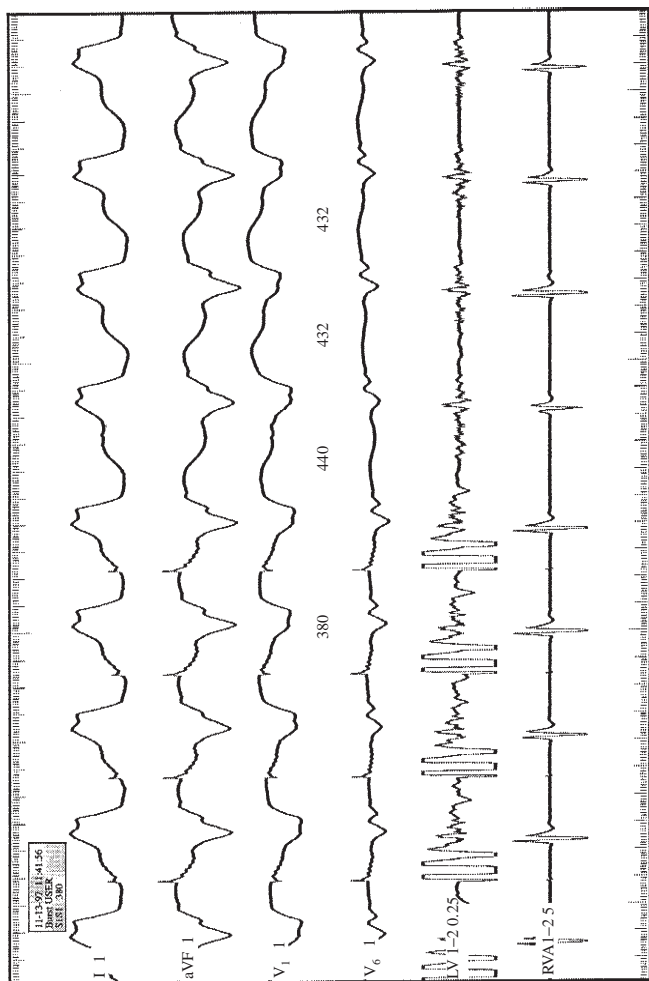


FIGURE 53.10 Entrainment of ventricular tachycardia. Pacing at a rate slightly faster (380 milliseconds) than tachycardia cycle length at a site believed to be the isthmus of the tachycardia resulted in QRS morphology very similar to the native ventricular tachycardia (concealed entrainment) in all 12 leads (only 4 leads shown). In addition, the post-pacing interval is very close to the tachycardia cycle length, suggesting that the pacing site is within the tachycardia circuit. Application of radiofrequency energy at this site resulted in successful ablation of this tachycardia. LV, left ventricular; RVA, right ventricular apex.

ACKNOWLEDGMENTS: *The author thanks Dr. Carlos Alves and Dr. Eduardo B. Saad for their contributions to prior editions of this chapter.*

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Cardiac Pacing

- I. INTRODUCTION.** The indications and technology of cardiac pacing continue to evolve, leading to a rapid increase in the number of pacemakers implanted. Pacemaker implantation rates increased from 329 implants per million population in 1990 to 612 per million population in 2002. In 2011, 400,000 cardiac devices were implanted and over 3 million people in the United States had implantable cardiac rhythm management devices. It is imperative that the physician caring for the pacemaker patient understand the basic physiology and technology of cardiac pacing and be able to apply these principles to effectively manage the unique problems with which these patients may present.

II. BASIC COMPONENTS OF CARDIAC PACEMAKERS

A. Pulse generator

1. **Power source (battery).** Lithium iodide is the most common chemical compound used. Lithium batteries deplete over a more predictable time course than other types of compounds, such as zinc mercuric oxide, that were used in prior generations of devices.
2. **Circuitry**
 - a. **Output circuits.** These circuits control programmable features of the output pulse, including amplitude and pulse width.
 - b. **Sensing circuits.** These circuits process the intracardiac electrogram, including amplification and filtering of the signal, and also provide other functions such as management of external electromagnetic interference (EMI). A bandpass filter allows signals of a certain frequency range to be passed while signals of other frequency ranges are blocked or attenuated. Pacemakers use a bandpass filter to distinguish between cardiac depolarization and repolarization signals from extracardiac signals, such as myopotentials from the chest wall musculature. Some appropriate signals that pass through the filter are small in amplitude, and a sense amplifier increases the appropriate signal for the device to process.
 - c. **Timing circuits.** These circuits control the pacing intervals and sensing/refractory periods. They may be altered by input from the sensing circuits.
 - d. **Telemetry circuit.** These circuits allow communication between an external programmer and the pulse generator for pacemaker programming or retrieval of information.
 - e. **Microprocessor.** Most modern pacemakers have computer chips with memory (read only memory [ROM] and random access memory [RAM]) and therefore have enhanced capabilities, such as downloading of new features via telemetry and increased storage of diagnostic data.
 - f. **Sensor circuit for rate-adaptive pacing.** See below.

B. Lead system

1. **Terminal pin.** The male portion of the proximal lead that connects to the pulse generator.

2. **Lead body.** Consists of conductor(s) and insulation. The conducting wire connects the stimulating and sensing electrodes to the terminal pin. The lead insulation is most commonly silicone rubber or a polyurethane material.
 3. **Stimulating/sensing electrode(s).** The distal end of the lead that connects via a fixation mechanism to atrial or ventricular myocardium.
 4. **Fixation device.** Passive fixation represents an attachment mechanism (e.g., “fins” or “tines”) that anchors electrodes to the endocardial trabeculae. Active fixation leads are secured to the endocardium using a “screw-in” mechanism. Over the past decade, active fixation leads have been implanted much more commonly. These types of leads have a lower rate of early dislodgement and yet higher chronic capture thresholds than passive fixation leads.
- C. **Polarity.** This refers to the electrode configuration of the pacing lead or the configuration of the pulse generator. Polarity may be unipolar or bipolar; however, some pacemakers can be programmed to pace in one polarity and sense in another (only if a bipolar lead is present).
1. **Unipolar.** Configuration in which the cathode (negative) is on the lead, usually the lead tip, and the anode (positive) is the pacemaker can. This results in a large sensing “antenna” and produces large pacemaker artifact (spikes) on the electrocardiogram (ECG) due to proximity of the circuit to ECG electrodes.
 - a. **Advantages.** Better sensing of premature ventricular contractions (PVCs), low-amplitude signals, and shifted axis.
 - b. **Disadvantages.** Oversensing of extraneous signals, especially pectoralis muscle activity (myopotentials), and inadvertent skeletal muscle stimulation may occur. Moreover, large pacemaker artifacts on the ECG may obscure native electrical activity.
 2. **Bipolar.** Both electrodes are at the end of the lead—the cathode (negative) at the distal tip and the anode (positive) at the proximal ring. This results in a smaller sensing “antenna” with smaller pacemaker artifact (spikes) on the ECG. Myocardial stimulation occurs as electrons from the cathode travel through the myocardium and back to the anode.
 - a. **Advantages.** Less myopotential oversensing and skeletal muscle stimulation, and the smaller pacemaker artifact on the ECG, do not obscure native wave morphology.
 - b. **Disadvantages.** More complex lead design is more susceptible to malfunction/failure. Small pacemaker artifact on the ECG may be difficult to see.
- D. **Lead–heart interface.** This is equivalent to the site of energy transfer (pacing) and sensing functions.

III. PACEMAKER CLASSIFICATION. The North American Society of Pacing and Electrophysiology and the British Pacing and Electrophysiology Group initially published a “pacemaker code” in 1983. Guidelines were later revised in 2002 and the five-position code remains the accepted nomenclature for pacemaker therapy (see Table 54.1). The first two positions (chamber paced and chamber sensed) are straightforward. The third position, however, is often misunderstood. As outlined in Table 54.1, the third position reflects the device response to a sensed event (labeled “I,” “T,” or “D”). “I” (Inhibited)—the device will pulse the given chamber unless it senses an intrinsic event. Thus when programmed DDI, atrioventricular (AV) synchrony will only exist if the atrial chamber is paced. If the atrial activity is intrinsic and the ventricular response depends only on the sensed activity in that chamber, then AV synchrony will not be provided. “T” (Triggered)—this mode is used during device testing where a sensed event results in the device producing a pulse. “D” (Dual)—atrial and ventricular sensing and pacing with dual-chamber devices. When programmed DDD, a sensed atrial beat inhibits atrial pacing and, after a programmed time interval, triggers ventricular pacing. This mode enables tracking of intrinsic atrial activity and corresponding ventricular pacing to allow AV synchrony.

TABLE 54.1 Revised NASPE/BPEG Generic (NBG) Code for Antibradycardia, Adaptive Rate, and Multisite Pacing

Position	I	II	III	IV	V
Category	Chamber(s) paced	Chamber(s) sensed	Response to sensing	Programmability, rate modulation	Multisite pacing
Letters	0 = none	0 = none	0 = none	0 = none	0 = none
	A = atrium	A = atrium	T = triggered	R = rate modulation	A = atrium
	V = ventricle	V = ventricle	I = inhibited		V = ventricle
	D = dual (A + V)	D = dual (A + V)	D = dual (T + I)		D = dual (A + V)
Manufacturers' designation only	> S = single (A or V)	S = single (A or V)			

BPEG, British Pacing and Electrophysiology Group; NASPE, North American Society of Pacing and Electrophysiology. *Pacing Clin Electrophysiol.* 2002;25:260–264.

IV. INDICATIONS FOR PACEMAKER IMPLANTATION. The American College of Cardiology (ACC)/American Heart Association (AHA)/Heart Rhythm Society (HRS) published updated guidelines for indications for pacemaker implantation in device-based therapy of cardiac rhythm abnormalities in 2008 (see Table 54.2).

V. PHYSIOLOGY OF CARDIAC PACING

- A. Pulse generator output.** This is determined by the output voltage and duration of the stimulating pulse (pulse width). Most implanted cardiac pacemakers use constant-voltage output (as opposed to most temporary cardiac pacemakers, which use constant-current output).
- B. Strength–duration relation.** There is an exponential relationship between the stimulus amplitude for myocardial stimulation and the pulse width, such that there is a rapidly rising strength–duration curve at pulse widths < 0.25 millisecond and a flatter curve at pulse widths > 1.0 millisecond (see Fig. 54.1).
 - 1. Rheobase.** The flattened portion of the strength–duration curve indicating the point at which increasing pulse width is no longer associated with a progressive decrease in stimulus amplitude (voltage) required for myocardial stimulation. In general, the rheobase voltage is determined by assessing the threshold stimulus voltage at a pulse width of 2.0 milliseconds.
 - 2. Chronaxie.** This corresponds to the threshold pulse width at twice the rheobase voltage. The chronaxie pulse duration approximates the point of minimal threshold energy on the strength–duration curve.
- C. Safety margins**
 - 1. Voltage.** The voltage output should be programmed to a level that is approximately twice the capture (stimulation) threshold for a 2:1 output safety margin.
 - 2. Pulse width.** The pulse duration should be programmed to a level approximately three times the pulse width capture threshold for a 3:1 output safety margin. The typical range for pulse width is 0.2 to 1.0 millisecond.
- D. Temporal changes in stimulation threshold.** Typically, the stimulation threshold rises within 24 hours following implantation of a permanent pacemaker lead. The

	Class I	Class II	Class III
SND	<ol style="list-style-type: none"> 1. SND with documented symptomatic bradycardia, including frequent sinus pauses that produce symptoms. 2. Symptomatic chronotropic incompetence. 3. Symptomatic sinus bradycardia that results from required drug therapy for medical conditions. 	<p>Ila:</p> <ol style="list-style-type: none"> 1. SND with heart rate < 40 bpm when a clear association between significant symptoms consistent with bradycardia and the actual presence of bradycardia has not been documented. <p>Ilb:</p> <ol style="list-style-type: none"> 2. Syncope of unexplained origin when clinically significant abnormalities of sinus node function are discovered or provoked in electrophysiological studies. <p>Ilb:</p> <p>In minimally symptomatic patients with chronic heart rate < 40 bpm while awake.</p>	<ol style="list-style-type: none"> 1. Permanent pacemaker implantation is not indicated for SND in asymptomatic patients. 2. Permanent pacemaker implantation is not indicated for SND in patients for whom the symptoms suggestive of bradycardia have been clearly documented to occur in the absence of bradycardia. 3. Permanent pacemaker implantation is not indicated for SND with symptomatic bradycardia due to nonessential drug therapy.
Acquired AV block	<ol style="list-style-type: none"> 1. Permanent pacemaker implantation is indicated for third-degree and advanced second-degree AV block at any anatomic level associated with the following conditions: <ul style="list-style-type: none"> — bradycardia with symptoms (including heart failure) or ventricular arrhythmias presumed to be due to AV block. — arrhythmias and other medical conditions that require drug therapy that results in symptomatic bradycardia. — awake, symptom-free patients in sinus rhythm, with documented periods of asystole ≥ 3.0 s or any escape rate < 40 bpm, or with an escape rhythm that is below the AV node. 	<p>Ila</p> <ol style="list-style-type: none"> 1. Permanent pacemaker implantation is reasonable for persistent third-degree AV block with an escape rate > 40 bpm in asymptomatic adult patients without cardiomegaly. <p>Ilb:</p> <ol style="list-style-type: none"> 2. Permanent pacemaker implantation is reasonable for asymptomatic second-degree AV block at intra- or infra-His levels found at electrophysiological study. 	<ol style="list-style-type: none"> 1. First-degree AV block. 2. Asymptomatic type I second-degree AV block at the supra-His (AV node) level or that which is not known to be intra- or infra-Hisian. 3. AV block that is expected to resolve and is unlikely to recur (e.g., drug toxicity, Lyme disease, or transient increases in vagal tone or during hypoxia in sleep apnea syndrome in the absence of symptoms).

TABLE 54.2

Indications for Cardiac Pacing

	Class I	Class II	Class III
	<p>— awake, symptom-free patients with AF and bradycardia with one or more pauses of at least 5 s or longer</p> <p>— after catheter ablation of the AV junction</p> <p>— postoperative AV block that is not expected to resolve after cardiac surgery.</p> <p>— neuromuscular diseases with AV block, such as myotonic muscular dystrophy, Kearns-Sayre syndrome, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy, with or without symptoms.</p> <p>Permanent pacemaker implantation is indicated for second-degree AV block with associated symptomatic bradycardia regardless of type or site of block.</p> <p>Permanent pacemaker implantation is indicated for asymptomatic persistent third-degree AV block at any anatomic site with average awake ventricular rates of 40 bpm or faster if cardiomegaly or LV dysfunction is present or if the site of block is below the AV node.</p> <p>Permanent pacemaker implantation is indicated for second- or third-degree AV block during exercise in the absence of myocardial ischemia.</p> <p>Permanent pacing is indicated for SND or AV block in patients with HCM</p>	<p>1b</p> <p>1. Neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with any degree of AV block (including first-degree AV block), with or without symptoms, because there may be unpredictable progression of AV conduction disease.</p> <p>2. AV block in the setting of drug use and/or drug toxicity when the block is expected to recur even after the drug is withdrawn.</p>	<p>1. Permanent pacemaker implantation is not indicated for patients who are asymptomatic or whose symptoms are medically controlled.</p>
Hypertrophic CM		Ila: None	

(Continued)

Class I	Class II	Class III
<p>Post MI</p> <ol style="list-style-type: none"> 1. Permanent ventricular pacing is indicated for persistent second-degree AV block in the His-Purkinje system with alternating bundle branch block or third-degree AV block within or below the His-Purkinje system after ST-segment MI. 2. Transient advanced second- or third-degree infranodal AV block and associated bundle branch block. If the site of block is uncertain, an electrophysiological study may be necessary. 3. Persistent and symptomatic second- or third-degree AV block. 	<p>1Ib: Permanent pacing may be considered in medically refractory symptomatic patients with HCM and significant resting or provoked LV outflow tract obstruction. (<i>Level of Evidence: A</i>) As for class I indications, when risk factors for SCD are present, consider a DDD ICD</p> <p>1Ia: None</p> <p>1Ib: Persistent second- or third-degree AV block at the AV node level, even in the absence of symptoms</p>	<p>2. Permanent pacemaker implantation is not indicated for symptomatic patients without evidence of LV outflow tract obstruction.</p> <ol style="list-style-type: none"> 1. Transient AV block in the absence of intraventricular conduction defects. 2. Transient AV block in the presence of isolated left anterior fascicular block. 3. New bundle branch block or fascicular block in the absence of AV block. 4. Persistent asymptomatic first-degree AV block in the presence of bundle branch or fascicular block.
<p>Chronic bifascicular and trifascicular block</p> <ol style="list-style-type: none"> 1. Advanced second-degree AV block or intermittent third-degree AV block. 2. Type II second-degree AV block. 3. Alternating bundle branch block. 	<p>1Ia: Syncope not demonstrated to be due to AV block when other likely causes have been excluded, specifically VT.</p> <p>2. Incidental finding at electrophysiological study of a markedly prolonged HV interval (≥ 100 ms) in asymptomatic patients.</p>	<ol style="list-style-type: none"> 1. Fascicular block without AV block or symptoms. 2. Fascicular block with first-degree AV block without symptoms.

TABLE 54.2

Indications for Cardiac Pacing (Continued)

	Class I	Class II	Class III
Carotid sinus hypersensitivity (carotid sinus irritability) and neurally mediated syncope	Recurrent syncope caused by spontaneously occurring carotid sinus stimulation and carotid sinus pressure that induces ventricular asystole of more than 3 s.	<p>3. Incidental finding at electrophysiological study of pacing-induced infra-His block that is not physiological.</p> <p>IIb.</p> <p>1. Neuromuscular diseases such as myotonic muscular dystrophy, Erb dystrophy (limb-girdle muscular dystrophy), and peroneal muscular atrophy with bifascicular block or any fascicular block, with or without symptoms.</p>	<p>1. Hypersensitive cardioinhibitory response to carotid sinus stimulation without symptoms or with vague symptoms.</p> <p>2. Situational vasovagal syncope in which avoidance behavior is effective and preferred.</p>
Termination of tachyarrhythmias		<p>IIa:</p> <p>Syncope without clear, provocative events and with a hypersensitive cardioinhibitory response of 3 s or longer</p> <p>IIb: Significantly symptomatic neurocardiogenic syncope associated with bradycardia documented spontaneously or at the time of tilt-table testing.</p> <p>Symptomatic recurrent SVT that is reproducibly terminated by pacing when catheter ablation and/or drugs fail to control the arrhythmia or produce intolerable side effects.</p>	<p>Permanent pacing is not indicated in the presence of an accessory pathway that has the capacity for rapid anterograde conduction.</p>

(Continued)

TABLE 54.2 Indications for Cardiac Pacing (Continued)

	Class I	Class II	Class III
Prevention of tachycardia	Sustained pause-dependent VT, with or without QT prolongation.	IIa: High-risk patients with congenital long QT syndrome IIb: Prevention of symptomatic, drug-refractory, recurrent AF in patients with coexisting SND.	1. Permanent pacing is not indicated for frequent or complex ventricular ectopic activity without sustained VT in the absence of the long QT syndrome. 2. Permanent pacing is not indicated for torsade de pointes VT due to reversible causes. 3. Permanent pacing is not indicated for the prevention of AF in patients without any other indication for pacemaker implantation.
Pacing after cardiac transplantation	Persistent inappropriate or symptomatic bradycardia not expected to resolve and for other class I indications for permanent pacing.	IIa: None IIb: 1. Relative bradycardia is prolonged or recurrent, which limits rehabilitation or discharge after postoperative recovery from cardiac transplantation. 2. Syncope after cardiac transplantation even when bradyarrhythmia has not been documented.	

AF, atrial fibrillation; AV, atrioventricular; CM, cardiomyopathy; HCM, hypertrophic cardiomyopathy; ICD, implantable cardioverter-defibrillator; LV, left ventricular; MI, myocardial infarction; SCD, sudden cardiac death; SND, sinus node dysfunction; SVT, sustained ventricular tachycardia; VT, ventricular tachycardia.

Class I: Conditions for which there is evidence and/or general agreement that pacing is beneficial, useful, and effective.

Class II: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of pacing.

Class IIa: Weight of evidence/opinion is in favor of usefulness/efficacy.

Class IIb: Usefulness/efficacy is less well established by evidence/opinion.

Class III: Conditions for which there is evidence and/or general agreement that pacing is not useful/effective and in some cases may be harmful.

From Epstein AE, DiMarco JP, Ellenbogen KA, et al. 2008 ACC/AHA/HRS guidelines for device-based therapy. *J Am Coll Cardiol*. 2008;51:e1–e62.

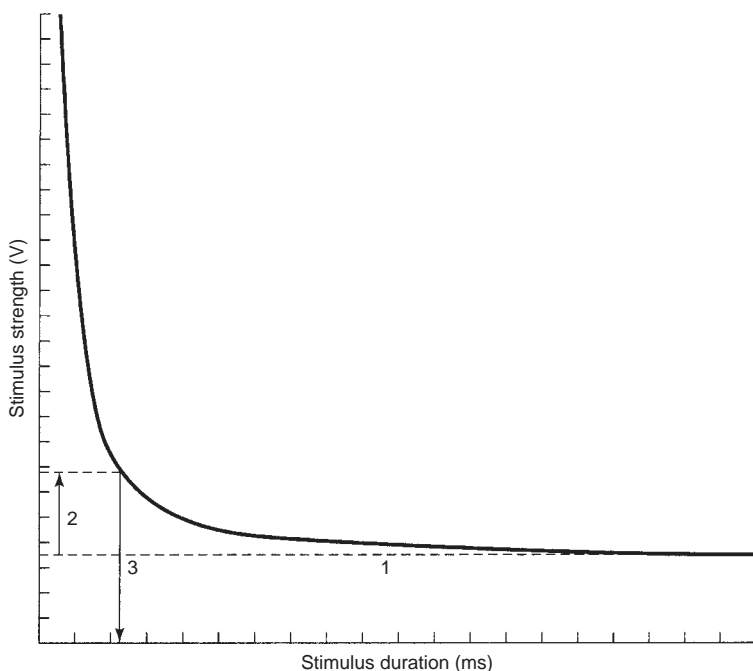


FIGURE 54.1 Strength-duration curve.

threshold peaks at 1 to 2 weeks, then gradually declines and plateaus at approximately 6 weeks at a level less than the acute peak, but greater than that measured at implantation. The absolute value of the temporal changes in stimulation thresholds varies between individuals and also between various types of electrodes.

VI. PACEMAKER TIMING CYCLES AND INTERVALS

A. Timing circuits. A pacemaker can be thought of as a series of timing circuits. An understanding of how these timing circuits interact can facilitate the analysis of pacemaker rhythms. The timing circuit runs until the cycle is completed or until it is reset. Completion of a timing cycle results in the release of a pacing output or the initiation of another timing cycle. Figure 54.2 illustrates the basic timing cycles and intervals for a dual-chamber pacemaker. The basic terms and abbreviations used for the pacemaker timing cycles and refractory periods are defined in the glossary.

B. Base rate behavior

1. Single-chamber pacemakers have a timing circuit that either is inhibited (reset) by a sensed native heartbeat or completes its cycle with a stimulus output. Dual-chamber pacemakers are more complex and incorporate more timing circuits. Figure 54.2 illustrates the timing cycles of a dual-chamber pacemaker in DDD mode. In general, base rate (lower rate) pacing for dual-chamber pacemakers involves two timing circuits.
 - a. The first timing circuit is the interval from a ventricular sensed or paced event to an atrial-paced event (atrial escape interval or AEI).

a paced beat. For example, the device sets the hysteresis rate at 50 bpm while the basal rate is 60 bpm. Therefore, if the patient's intrinsic rate is > 50 bpm, the device will not pace. However, if the patient's rate falls below 50 bpm, the pacer will pace at 60 bpm. As hysteresis can appear as an unusually long delay on the ECG strip, it can be misinterpreted as failure to pace or as inappropriate sensing.

C. Upper rate behavior

1. As the sinus rate accelerates, the sensed atrial events terminate the AEI and initiate the AVI. The result is P-wave synchronous ventricular pacing (unless the PR interval is shorter than the PV interval, in which case pacing will be fully inhibited).
2. The maximal atrial rate that a dual-chamber pacemaker can sense is determined by the total atrial refractory period (TARP). As defined earlier in this chapter, the TARP is composed of the AVI and the postventricular atrial refractory period (PVARP). The PVARP is an interval during which the atrial channel can see incoming signals, but will not respond to them. However, because signals are seen in PVARP, the pacer can use advanced features to assess whether high atrial rates are occurring. As the sinus rate accelerates, the native atrial intervals become shorter than the TARP, and some atrial events will not be sensed. An abrupt, fixed block occurs as the pacemaker only intermittently senses the P-waves, which may result in symptoms as the rate drops precipitously.
3. Maximal tracking rate interval (MTRI) or upper rate limit is an additional timing circuit designed to avoid abrupt blocks at upper pacing rates. It works in conjunction with the AVI to determine the highest ventricular pacing rate that can be achieved in response to atrial sensed events. A sensed atrial event initiates the AVI and the MTRI.
 - a. If the AVI completes its cycle and the MTRI has also completed its cycle, then a ventricular output occurs at the programmed AV interval.
 - b. If the AVI completes its cycle and the MTRI has not completed its cycle, then the ventricular output is delayed until the MTRI has timed out. This prolongs the PV interval and allows continued tracking of the atrial rate. However, the longer PV interval also places the ventricular output closer to the following P-wave.
 - c. If the sinus rate accelerates to a sufficient rate, the delayed ventricular output may cause the following P-wave to fall within the PVARP and not be sensed. The result is an intermittent "dropped" beat and a pause similar to Wenckebach behavior. However, abrupt block is less likely. More modern pacemakers may incorporate features designed to limit the degree of fixed block at the upper rate limit, such as rate smoothing (adjustment of the AEI as the PV interval changes) and rate-responsive AV delay. However, fixed block at the upper rate limit may still occur, particularly if the device is suboptimally programmed.

VII. RATE-ADAPTIVE PACING. The primary purpose of rate-adaptive pacing is to emulate the function of the sinus node for patients with chronotropic incompetence or atrial arrhythmias that preclude reliable sensing of native sinoatrial rhythm. This function is expressed with the letter "R" in the fourth position (AAIR, VVIR, DDDR, and so on).

A. Primary components of a rate-adaptive pacemaker system

1. A sensor located in the pacing lead or pacemaker itself detects a physical or physiologic parameter that is directly or indirectly related to metabolic demand.
2. Rate-modulating circuitry within the pacemaker contains an algorithm that translates a change in the sensed parameter to a change in the pacing rate.
3. Algorithm programmability such that a physician can make adjustments to accommodate the heart rate requirements of the individual patient.

TABLE 54.3 Sensors in Rate-Responsive Pacing

Methods	Physiologic parameters	Mechanism	Advantages	Disadvantages
Impedance sensing	Respiratory rate Minute ventilation Stroke volume	Impedance plethysmography	Highly physiologic Highly proportional to metabolic demand	Delayed response Susceptible to electrode motion artifact
Ventricular evoked response	Evoked QT interval (stim-T interval)	Reflects catecholamines	More physiologic	Requires ventricular pacing
Vibration, acceleration, gravitation, motion sensing	Body movement	Piezoelectric element	Rapid response No special lead needed	Nonphysiologic and nonspecific Late plateau response
Special sensors on pacing electrode	Central venous temperature ^a dP/dt^b Mixed venous oxygen saturation ^b	Thermistor Piezoelectric element Optical sensor	More physiologic	Complex lead

^aNo longer produced, although still in use in Japan.

^bPresently available only in clinical trials.

Adapted from Lau, Chu-Pak. The Range of Sensors and Algorithms Used in Rate Adaptive Cardiac Pacing. *PACE*, 1992; 1177–1190.

4. Pacemakers can set the sensor to on or off. Some pacemakers can be put in a passive mode in which they store information in order to predict how the pacer would act if set to rate-responsive behavior.

B. Basic technical categories of pacemaker sensors (see Table 54.3). Motion sensors are the most commonly used due to their simplicity, speed of response, and compatibility with standard unipolar and bipolar pacing leads. Other sensors are more physiologic but may require technically complex pacing leads. Of the physiologic sensors, only the minute ventilation type is widely available. Minute ventilation sensors are prone to interference from electromagnetic sources, coughing, hyperventilation, and arm swinging.

VIII. AUTOMATIC MODE SWITCHING. Automatic mode switching is a programmable response of a dual-chamber pacemaker during an atrial tachyarrhythmia (atrial tachycardia, atrial fibrillation, or atrial flutter) designed to avoid nonphysiologic ventricular pacing due to atrial tracking. Generally, the device switches from a DDD mode to a VVI mode, usually with a gradual reduction of the pacing rate. The device switches back to the DDD mode after the atrial tachyarrhythmia resolves. Mode switch information can also be helpful in documenting atrial arrhythmia burden in order to help dictate medical therapy for arrhythmias.

IX. BASIC PACING MODES. The choice of pacemaker generator and the mode of pacing depend mainly on the underlying rhythm disturbance and whether AV synchrony and rate response are desired (see Table 54.4).

TABLE 54.4 Guidelines for Choice of Pacemaker Generator in Selected Indications for Pacing

	Sinus node dysfunction	AV block	Neurally mediated syncope or carotid sinus hyperreactivity
Single-chamber atrial pacemaker	No suspected abnormality of AV conduction and not at increased risk for future AV block Maintenance of AV synchrony during pacing if desired RR if desired	Not appropriate	Not appropriate (unless AV block systematically excluded)
Single-chamber ventricular pacemaker	Maintenance of AVS during pacing not necessary RR available if desired	Chronic AF or other atrial tachyarrhythmia or maintenance of AVS not necessary RR available if desired	Chronic AF or other atrial tachyarrhythmia RR available if desired
Dual-chamber pacemaker	AVS during pacing desired Suspected abnormality of AV conduction or increased risk of AV block	AVS during pacing desired Atrial pacing desired RR available if desired	Sinus mechanism present RR available if desired
Single-lead, atrial-sensing ventricular pacemaker	Not appropriate	Normal sinus function and no need for atrial pacing Desire to limit the number of pacemaker leads	Not appropriate

AF, atrial fibrillation; AV, atrioventricular; AVS, atrioventricular synchrony; RR, rate response.

- A. Ventricular demand pacing (VVI).** This remains the most commonly used pacing mode worldwide. Although VVI pacing protects the patient from lethal bradycardias, AV synchrony is not restored or maintained nor does it provide rate responsiveness in the patient with chronotropic incompetence. Because AV synchrony is absent, the rate of pacemaker syndrome is high (up to 83% in randomized trials).
- B. AAI (atrial demand pacing).** This mode is appropriate for patients with sinus node dysfunction who have intact AV conduction. A sensed atrial event will inhibit atrial pacing, and expiration of a preset AA interval will pace the atrium at a preset rate. Because there will be no ventricular support if AV block should occur, careful testing of AV conduction is necessary at the time of pacemaker implantation (incremental atrial pacing). This mode is infrequently used in the United States.
- C. AV sequential pacing**
 - 1. DDI.** There are both atrial and ventricular sensing and pacing, but no atrial tracking can occur. The pacemaker rate is therefore fixed, and this mode is rarely used.

2. **VDD.** In this mode, ventricular stimulation can either be inhibited by a spontaneous ventricular beat or be initiated by an atrially tracked beat, and it can therefore be used in patients with normal sinus function but impaired AV conduction. This modality uses a “floating” sensing electrode on the atrial portion of the ventricular lead, but it is altogether rarely used.
3. **DDD.** This system provides the most physiologic pacing mode. The pacer can be totally inhibited with normal sinus rhythm, can pace the atrium with spontaneous ventricular depolarization, can pace the ventricle in response to a spontaneous P-wave, and can sequentially pace both the atrium and ventricle. This system is most appropriate in patients who have impaired AV conduction with either an intact or dysfunctional sinus node.

X. BIVENTRICULAR PACING. Because patients with systolic left ventricular (LV) dysfunction and wide QRS complexes have dyssynergic contractility, the use of multisite atrial, right ventricular (RV), and LV pacing strategies has been proposed. For this purpose, an additional pacemaker lead is placed transvenously into the coronary sinus or epicardially during open chest surgery for simultaneous stimulation of the left and right ventricles.

- A. Biventricular cardiac resynchronization pacing for heart failure has been accepted as standard therapy for patients with a depressed ejection fraction ($EF < 35\%$), QRS duration > 120 milliseconds, and NYHA class III or IV symptoms despite appropriate medical therapy. Several randomized studies, including MUSTIC, MIRACLE, MIRACLE-ICD, PATH-CHF, and VENTAK-CHF/CONTAK-CD, have demonstrated improved functional status, exercise capacity, and quality of life with biventricular pacing. CARE-HF demonstrated a decrease in the primary end point of death and hospitalization with biventricular pacing (see Chapter 56) in heart failure patients with depressed systolic function, class III/IV symptoms, and wide QRS.
- B. Consideration for implantation of a biventricular pacemaker should be given for patients with LV dysfunction who will require a high percentage of ventricular pacing. This recommendation is based on the findings from the DAVID trial where high rates of RV pacing caused ventricular dyssynchrony and more hospitalization for congestive heart failure (CHF) or death.
- C. Although the overall rate of clinical improvement with biventricular pacing is high in these trials (about 70% of patients), it is not entirely clear how to identify patients who will respond ahead of time. Multiple echocardiographic and electrocardiographic measures have been investigated to help predict an individual patient's likelihood of clinical response, but so far no single modality has proven entirely reliable.

XI. PACEMAKER IMPLANTATION: PERTINENT ISSUES FOR THE PHYSICIAN

- A. **Preoperative issues.** Several issues must be addressed for the patient scheduled for routine pacemaker implantation.
 1. **History and physical examination.** Attention should be given to any findings that may affect the site and approach for pacemaker implantation, such as patient handedness (pacemakers are generally implanted on the contralateral side), history of mastectomy, presence of congenital abnormalities (e.g., anomalous venous drainage), current central venous lines, or tricuspid valve disease or surgery.
 2. **Informed consent** (risks, benefits, and alternatives)
 3. **Tests**
 - a. Posteroanterior and lateral chest radiograph.
 - b. Twelve-lead ECG should be obtained.
 - c. Blood tests may include serum electrolytes, complete blood count, creatinine, prothrombin/international normalized ratio (INR), and partial thromboplastin times.

4. Medications

- a. Most physicians prefer warfarin to be discontinued at least 3 days before the procedure. In some cases, such as primary implants or generator changes, coumadin can be kept close to therapeutic, with INR at approximately 2.0. Consider admission to hospital for intravenous heparin if the risk of discontinuation of anticoagulation is high. Heparin may be discontinued 4 to 6 hours before the procedure.
- b. The dosage of oral hypoglycemics or insulin may have to be adjusted.

5. Patient preparation

- a. The patient should have nothing by mouth for at least 6 to 8 hours before the procedure. Intravenous hydration should be initiated upon arrival to the laboratory to prevent hypovolemia, which may make venous cannulation more difficult.
- b. An intravenous catheter is particularly helpful if placed in the arm ipsilateral to the proposed pacemaker site. This allows the ability to perform a venogram if there is difficulty in obtaining venous access during pacemaker implantation.
- c. The patient should be shaved and cleansed (e.g., with povidone iodine) in the area from above the nipple line to the angle of the jaw and from the sternum to the axillary line on the side of the implantation site.
- d. Antibiotic prophylaxis before pacemaker implantation is a controversial issue, and various prospective studies have provided conflicting information. Some centers have advocated antibiotic prophylaxis with an agent active against staphylococci for patients at high risk for endocarditis, such as those with prosthetic valves or complex congenital heart disease, or for redo procedures or for prolonged or potentially contaminating procedures. Other centers use antibiotic prophylaxis routinely (systemically and/or locally).

B. Postoperative issues

1. **General recommendations.** Patients are usually admitted for overnight observation on telemetry after pacemaker implantation.
2. **Postoperative testing.** Posteroanterior and lateral chest radiograph should be obtained to document proper position of the pacemaker leads and connection of the terminal pins to the pulse generator. The radiograph should also be examined for evidence of pneumothorax, pericardial effusion, or pleural effusion.
3. **Resuming anticoagulation.** Anticoagulation should not be aggressive in the early post-implantation period due to the risk of pacemaker pocket hematoma, which has been associated with increased risk of complications such as reoperation and infection. Administration of therapeutic doses of unfractionated or low-molecular-weight heparin in the 48 hours following device implantation will increase the risk of hematoma and should generally be avoided. If warfarin was held prior to device implantation, it may be restarted the day prior to device implantation based on the INR.

4. Pacemaker evaluation

- a. Evaluation in the pacemaker clinic before discharge includes assessment of pacing and sensing thresholds and lead impedance. The pacemaker is programmed to optimize patient hemodynamics and minimize battery expenditure.
- b. Capture thresholds are expected to rise over the first 2 to 6 weeks after implantation. Therefore, the pacemaker should be programmed with an adequate safety margin to account for these changes.
- c. Rate adaptation for activity-sensing pacemakers may be programmed according to informal (e.g., hallway walking) or formal (e.g., treadmill) exercise testing.

5. Discharge planning

- a. **Discharge instruction.** Usually includes patient education regarding the recognition of pacemaker pocket complications, such as signs of infections,

bleeding, or hematoma. The patient is generally advised to avoid heavy lifting or vigorous activity (especially forceful abduction) with the arm ipsilateral to the implant site.

- b. The patient should be provided with information regarding his or her pacemaker, including a wallet card identifying the pacemaker and lead(s) manufacturer, model numbers, and serial numbers.
- c. The patient may be provided with and instructed in the use of a transtelephonic monitoring system for remote evaluation of the pacemaker.
- d. Endocarditis prophylaxis is generally *not* recommended routinely for patients with pacemakers, according to the updated AHA guidelines.

XII. COMMON PACEMAKER PROBLEMS

A. Acute complications of pacemaker implantation

1. Pneumothorax/Hemothorax

- a. This complication may be asymptomatic and detected only by chest radiograph. The diagnosis should be considered in a patient with dyspnea and/or pleuritic chest pain after implantation.
- b. A small pneumothorax may resolve without intervention. However, the presence of severe symptoms, a pneumothorax > 10%, or an expanding or persistent pneumothorax often necessitates placement of a chest tube.

2. Pacemaker pocket hematoma

- a. This is one of the most common complications of pacemaker implantation and is often due to small vessel venous bleeding inside the pacemaker pocket. Bleeding may also arise from arterial vessels or retrograde flow of venous blood along the pacemaker leads into the pocket.
- b. Signs and symptoms may include pain, swelling, and sometimes bleeding at the pocket site.
- c. Small hematomas may be managed conservatively with pressure dressings, elevation (head of bed at least 45°), and analgesics. The patient should be positioned on his or her side contralateral to the pacemaker site. Large hematomas may compromise the integrity of the incision site and result in dehiscence. The patient may require urgent surgical exploration and hematoma evacuation in the electrophysiology laboratory or operating room.
- d. Percutaneous insertion of a needle to drain a hematoma increases the risk of infection and should be avoided.

3. Cardiac or central venous perforation. Perforation may lead to pericardial effusion and cardiac tamponade and should be suspected in the patient with chest pain, pericardial friction rub, or hypotension after pacemaker implantation. A chest radiograph may reveal an enlarged cardiac silhouette or an extracardiac lead tip. A change in the paced ventricular morphology, particularly a right bundle branch pattern, may indicate ventricular lead migration. The hemodynamically unstable patient with tamponade will require urgent pericardiocentesis and drainage of the effusion.

4. Diaphragmatic stimulation. Stimulation of the left diaphragm may occur with a pacing lead at the RV apex, particularly at high pacing outputs. The possibility of cardiac perforation should be considered. Stimulation of the right diaphragm may occur due to stimulation of the right phrenic nerve by a displaced atrial lead. Reduction in the pacemaker output voltage or lead repositioning may be necessary.

5. Local muscular stimulation

- a. This may occur with a unipolar pacemaker configuration, particularly if the pulse generator is positioned upside down within the pocket (whereby a node is directly in contact with the pectoralis muscle).

- b. A pacing lead fracture may result in leakage of current into the surrounding tissue, resulting in local muscle stimulation.
6. **Pacemaker malfunction**
 - a. The pulse generator may be defective or may have been damaged at the time of implantation (e.g., by electrocautery or direct current [DC] defibrillation).
 - b. Improper fixation of the terminal pins of the pacing leads into the pulse generator (e.g., loose-set screws) may result in complete or intermittent pacemaker malfunction with high impedance measurements.
7. **Lead dislodgement or damage**
 - a. Pacing leads may become dislodged soon after implantation before the lead has a chance to become more fixed in place through clotting and fibrosis. Lead dislodgement may be suspected by noncapture, high lead impedance, undersensing, or oversensing on telemetry or ECG and may be confirmed by chest radiography or formal pacemaker testing.
 - b. The lead may be damaged at the time of implantation by forceful handling or excessively tight retention sutures.
 - c. Interrogation of a device with a damaged lead may reveal changes in impedance. A break in the insulation of the lead results in low impedance. A contained fracture of the lead conductor, poor terminal pin to device connection, or lead dislodgement all result in high impedance.
- B. **Chronic complications of pacemaker implantation**
 1. **Pacemaker system infection**
 - a. The reported incidence of pacemaker infection is 1.9 per 1,000 device-years based on a large cohort study spanning 30 years (1). As noted earlier, the number of pacemakers implanted annually continues to increase, and yet the rate of device-related infections is increasing at a disproportionately higher rate. Recognition of these infections and appropriate treatment is critical for health-care providers managing patients with cardiac implantable devices. The infection may involve only the pacemaker pocket or the entire system, with subsequent life-threatening sepsis. There is a higher incidence with repeat operations (e.g., pulse generator replacement). Causative organisms tend to be skin flora such as *Staphylococcus* species.
 - b. Treatment should include intravenous antibiotics; however, antibiotic therapy rarely eradicates the infection unless the pacemaker system is removed. In the largest study to date (1), mortality rates for device-related endocarditis range from 31% to 66% without device removal. Mortality improves to 18% or less with a combined approach of medical therapy and complete device removal.
 - c. The timing of system removal depends on the clinical status of the patient; however, prolonged delays should be avoided.
 2. **Intravascular thrombosis or obstruction**
 - a. Vascular complications are common with device therapy. They range from asymptomatic venous occlusion to extremity edema. Mortality from vascular complications is rare. Initial treatments may include heat and upper-extremity elevation. Symptomatic thrombosis of the subclavian or axillary veins may require anticoagulation or systemic thrombolytic therapy. It is recommended that documented deep venous thrombosis be treated with anticoagulation with warfarin for at least 6 months, unless contraindicated.
 - b. Superior vena cava stenosis or occlusion may require percutaneous balloon dilatation or surgical consultation for consideration of repair.
 3. **Twiddler's syndrome.** A condition in which the pacemaker is turned, usually unintentionally, upside down within the pacemaker pocket. The leads may become twisted, resulting in excessive traction on the leads and dislodgement.

XIII. PACEMAKER SYSTEM MALFUNCTION

- A. In assessing the patient with suspected pacemaker malfunction, it is important to interpret the ECG carefully. Ideally, intracardiac tracings obtained by pacemaker interrogation should be interpreted. Pacing artifacts or spikes are high-frequency signals and are often filtered out by newer digital surface ECG machines. Furthermore, pacing artifacts from bipolar leads are smaller and more difficult to see than artifacts from unipolar leads. It may be necessary to record multiple leads or use an older analogue recorder to clearly visualize the pacing artifact. Pseudomalfunction occurs when recording and digital artifacts are misinterpreted. Approaching the paced patient's ECG systematically will help to determine the appropriateness of pacing.
- B. **General evaluation for possible pacemaker malfunction**
 1. If a recent pacemaker interrogation is available, review the programmed parameters for the pacemaker, particularly the mode, base rate, upper rate limit, intervals, and the presence of other features such as automatic mode switching, hysteresis, rate-adaptive features, or managed ventricular pacing.
 2. Obtain a 12-lead ECG and evaluate the following:
 - (a) Determine whether pacing stimulus artifacts are present and whether the appropriate chamber is captured.
 - (b) If no pacing stimulus artifact can be seen, native depolarization should be adequate.
 - (c) Evaluate whether native beats are appropriately sensed in relation to paced complexes.
 - (d) Evaluate the timing cycles of a dual-chamber pacemaker by measuring backward from an atrially paced event, as described in Section VI.B.2.
- C. Patients with pacemaker system malfunction generally demonstrate absence of a pacing stimulus artifact, failure to capture, or failure to sense.
 1. **Failure of pacemaker stimulus output.** A differential diagnosis of the more common causes of pauses during a paced rhythm is listed later in this chapter. Application of a magnet over the pacemaker should result in asynchronous pacing. If the pauses resolve when the magnet is applied, then the diagnosis of oversensing is most likely. If the pauses do not resolve, then one of the other causes should be considered.
 - a. **Pulse generator failure.** The pulse generator may be at the end of life (EOL), which may easily be detected with a pacemaker check.
 - b. **Lead failure.** This can be due to loose-set screw or terminal pin disconnection, lead conductor failure, or lead insulation failure. Suspicion of lead malfunction should prompt the clinician to obtain a chest radiograph. This may reveal the terminal pin not situated properly within the header of the pulse generator or it may demonstrate a defect in the lead insulation or conductor coil. A significant increase in the lead impedance suggests lead conductor failure, and a significant decrease in the lead impedance suggests lead insulation failure.
 - c. **Oversensing.** EMI, myopotentials, cross talk, or T-wave oversensing can lead to falsely interpreted signals.
 - d. **Pseudomalfunction.** Pacemaker malfunction can be mistakenly diagnosed if the small spikes from a bipolar system are not appreciated on the surface ECG. Malfunction can also be diagnosed mistakenly if attention is not paid to additional features that allow the heart rate to fall below or above the set base rate. It is important to remember additional features such as hysteresis, sleep settings, rate-adaptive behaviors, or automatic mode switch, each of which can be mistaken for pacemaker malfunction.
 2. **Failure to capture**
 - a. **Elevated capture threshold.** Electrolyte disturbance (e.g., hyperkalemia and acidemia), antiarrhythmic drugs (particularly class Ic agents such as

flecainide), and myocardial fibrosis (e.g., cardiomyopathy and myocardial infarction [MI]) can increase the capture threshold.

b. Lead malfunction

(1) Lead fracture.

(2) Lead dislodgement or perforation may result in a change in the paced morphology, especially a change from left to right bundle branch morphology.

c. Exit block. Exit block is defined as failure of the pacing output at the distal electrode to stimulate adjacent myocardium. This is often caused by the inflammatory reaction that occurs at the pacemaker lead tip at the time of implantation. It occurs in approximately 5% of cases and may be managed with systemic steroids. Most pacing leads have steroid-eluting electrodes designed to minimize the degree of inflammation at the electrode tip and decrease the incidence of exit block.

d. Latency. Defined as the delay between the delivery of an output pulse and the onset of electrical systole, such as occurs with severe electrolyte disturbances.

e. Pseudomalfuction. Artifact with small spikes on the surface ECG, such as occurs when the patient's refractory periods interfere with pacer function.

3. Failure to sense

a. Lead dislodgement is usually accompanied by failure to capture (see discussion in Section XIII.C.2)

b. Lead insulation failure (see discussion in Section XIII.C.1)

c. Inadequate endocardial signal

d. Change in electrogram. Transient changes may occur due to electrolyte or acid-base disturbance, and permanent changes may occur due to MI or cardiomyopathy

e. Ectopic beats

f. Pulse generator failure (sensing circuits)

g. Functional undersensing. Defined as undersensing that occurs due to normal pacemaker function, such as refractory periods, blanking periods, or safety pacing.

D. Other pacemaker malfunctions

1. Pacemaker syndrome. Pacemaker syndrome is defined as the signs and symptoms that occur in the pacemaker patient because of inadequate timing of atrial and ventricular contractions. Pacemaker syndrome is commonly caused by retrograde ventriculoatrial (VA) conduction, which causes atrial contraction against closed mitral and tricuspid valves. Pacemaker syndrome may also occur during an exercise-induced atrial arrhythmia due to loss of AV synchrony when a device with an automatic mode-switching feature converts to VVI pacing.

2. Pacemaker-mediated tachycardia (PMT). This is defined as a paced tachycardia that is sustained by the continued active participation of the pacemaker in the rhythm. At first glance, the resultant wide-complex (paced) tachycardia may appear to be ventricular tachycardia, especially for pacemakers with bipolar leads where the pacing artifact may be difficult to discern on ECG.

a. One form of PMT is the rapid ventricular pacing that occurs as a dual-chamber pacemaker attempts to track the rapid atrial rate during an atrial tachyarrhythmic episode.

b. Another form of PMT occurs when there is oversensing in the atrial channel, such as myopotentials.

c. Endless-loop tachycardia (ELT). PMT in which a repetitive sequence of sensing of retrograde atrial activity results in triggering of a ventricular paced beat at the end of the MTRI. ELT requires a trigger for initiation, which may be any event that results in AV dissociation and allows retrograde VA

conduction to occur after a native or paced ventricular beat. The trigger may be a PVC, atrial undersensing, atrial oversensing, or atrial noncapture. ELT is sustained until there is VA block. Application of a magnet over the pacemaker will terminate ELT. The most reliable way to prevent ELT is to program the PVARP to a value that exceeds the VA conduction interval. Some of the more modern pacemakers have PMT or ELT recognition and termination algorithms designed to prevent and/or terminate PMT and ELT.

XIV. COMMON ISSUES FOR THE PATIENT WITH A PACEMAKER

A. Perioperative patient

1. **Preoperative assessment.** Review of pertinent history and a physical examination should be performed. The patient should undergo a pacemaker evaluation to assess the programmed parameters, pacing and sensing thresholds, and lead impedance.
2. The degree of pacemaker dependence should be determined. A patient who is pacemaker-dependent should have temporary pacing equipment readily available.
3. If the operative field is in the area near the pacemaker, the rate response feature of the pacemaker should be deactivated to avoid inappropriate rapid pacing due to vibrations or pressure transmitted to the pulse generator.
4. Electrocautery may result in temporary inhibition of pacemaker output due to oversensing of the EMI. Electrocautery should be used sparingly and in short bursts, and the cautery electrode should be placed at a distance from the pacemaker site.
5. Postoperatively, the pacemaker should be reevaluated for any sign of malfunction, the presence of a reset mode, and any change in lead threshold or impedance values. A chest radiograph should be obtained after cardiac surgery to evaluate for lead damage or dislodgement.

B. EMI in the hospital environment

1. **Magnetic resonance imaging (MRI).** The magnetic field generated by the electromagnet and the radiofrequency signal produced to modulate the magnetic field for MRI may cause torque forces or malfunction of cardiac pacemakers. More modern pacemakers contain fewer ferromagnetic components than previous pacemakers, so that torque forces are less common. The magnetic forces may close the pacemaker reed switch and result in asynchronous pacing. The radiofrequency signal may result in inhibition of pacing, rapid pacing, or reversion to reset mode. Unipolar pacemakers are more susceptible to interference from MRI. While a small number of centers have developed specific scanning protocols for patients with cardiac implantable electronic devices (CIEDs), in general, MRI should be avoided in most pacemaker patients unless absolutely necessary.

Recently, MRI conditional pacemaker systems have emerged. Specifically, the RevoMRI SureScan System has been evaluated in a clinical trial (EnRhythm MRI SureScan Pacing System Study) and is now widely available for use in clinical practice. Of the 211 enrolled patients who underwent an MRI 9 to 12 weeks after receiving the device, no MRI-related complications were reported. As new applications for MRI continue to emerge in clinical practice, recent estimates suggest that as many as 50% to 75% of patients with CIED will have an indication for MRI during their lifetime. MRI conditional technology will undoubtedly continue to evolve and is likely to become standard in new pacemaker systems from all major manufacturers.

2. **Extracorporeal shock-wave lithotripsy (ESWL)**

- a. ESWL is a treatment for renal calculi that involves the production of focused hydraulic shock waves from an underwater spark gap. Interference or damage to a pacemaker may occur due to the spark gap or the shock

waves. Activity-based rate adaptation pacemakers with piezoelectric crystals may be damaged by the shock waves, and the shock waves may cause oversensing and subsequent nonphysiologic rapid pacing rates. Such pacemakers should be reprogrammed with the rate-adaptive feature deactivated before the procedure. If the pacemaker with a piezoelectric crystal is located in the abdomen, then ESWL should not be performed.

- b. The shock waves may be misinterpreted as atrial activity; therefore, dual-chamber pacemakers should be programmed to VVI mode to avoid rapid ventricular pacing.
- c. A patient with a pacemaker may undergo ESWL; however, the pulse generator should be as far as possible from the focal point of the lithotripsy shock waves, and a cardiologist who is experienced in pacemaker management should be available nearby during the procedure.

3. Radiation therapy

- a. Diagnostic radiation does not interfere with cardiac pacemakers. Therapeutic radiation therapy to the thorax such as that used for breast or lung malignancies may result in interference and/or cumulative damage. The damage to the integrated circuitry of the pacemaker results from leakage currents between the insulated parts. This damage is directly related to the cumulative radiation dose.
 - b. The pacemaker should be assessed before and after a treatment session. ECG monitoring is recommended for patients who are pacemaker-dependent. The pulse generator should be shielded from the ionizing radiation or moved to another site if necessary.
4. **Cardiac monitors.** Cardiac monitors that inject current into the patient's body in order to measure minute ventilation may interfere with pacemakers that use minute ventilation for rate adaptation.
 5. **Transcutaneous electric nerve stimulation** is considered safe for patients with bipolar pacemakers. Patients with unipolar pacemakers may require a reduction in sensitivity.
 6. **Dental equipment.** Some types of dental equipment may cause pacemaker inhibition, particularly for unipolar pacemakers. Vibrations may increase the pacing rate of activity-sensing rate-adaptive pacemakers.
 7. **Cardioversion/defibrillation.** The shock from a DC cardioversion or defibrillation may cause damage to the pulse generator or result in the device being reset. If DC cardioversion or defibrillation is necessary, the patch electrodes should be positioned as far as possible from the pulse generator. A pacemaker evaluation should be performed after the procedure.
 8. **Electroconvulsive therapy** generally does not interfere with pacemaker function. The patient should have a pacemaker evaluation before and after each session. ECG monitoring during the session is prudent. Seizure activity during the procedure may produce myopotential inhibition of unipolar pacemakers.
 9. **Diathermy** may result in pacemaker interference or damage if applied to the region near the pulse generator.
 10. **Electrocautery** (discussed in Section XIV.A.4)

C. Environmental EMI

1. **Cellular telephones.** These devices are generally safe. Older models were reported to interfere with cardiac pacemakers while transmitting or receiving calls. A pacemaker patient should not carry a cellular telephone near the pacemaker site (i.e., shirt pocket) and should avoid holding the telephone to the ipsilateral ear during use.
2. **Electronic article surveillance (EAS)** is a type of antitheft system consisting of a gate that produces an electromagnetic field through which individuals must walk. The field may result in pacemaker interference, primarily inhibition of

pacemaker output. Patients with unipolar dual-chamber pacemakers are particularly susceptible to interference from EAS systems.

3. **Industrial electrical equipment.** This includes devices, such as arc welders, that may generate strong electrical fields. The strength of the electrical field varies among various types of equipment and if sufficiently strong may interfere with unipolar pacemakers. Patients may require individual environmental testing to ensure safety.
4. **Microwave ovens.** Due to better sealing of microwave ovens and improved shielding of pulse generators, interference with pacemakers by microwave ovens is no longer considered a significant problem.
5. **Metal detectors.** Although the metal detectors in public places such as airports may raise an alarm due to detection of a pacemaker, there is generally no significant interference with pacemaker function. Patients should avoid lingering around these devices and pass through them at a normal speed.
6. **High-voltage power lines and electrical substations.** These areas may cause inhibition or asynchronous pacing in unipolar pacemakers if the patient is quite close to the electrical field. At usual public distances from such areas, there should be no pacemaker interference.

D. Pacemaker response to EMI

1. **Pacing inhibition.** For obvious reasons, this may be catastrophic. The majority of pacemakers used today contain protective algorithms that make prolonged inhibition uncommon.
2. **Rapid pacing.** Oversensing of EMI by the atrial channel in a device set to DDD can cause the pacer to trigger ventricular pacing at or near the upper tracking limit. This response is usually well tolerated, but in certain individuals when sustained it may cause palpitations, hypotension, or angina. Rapid pacing may also occur via activation of minute ventilation sensors.
3. **Reversion to asynchronous pacing.** Most pacers have algorithms that protect against prolonged inhibition from noise. Algorithms are based upon the principle that detected rapid frequency signals are unlikely to represent myocardial activation. The pacemaker is programmed to have a noise sampling window during the ventricular refractory period. In most devices, repetitive signaling detected in the noise sampling window reverts the device to asynchronous pacing. Asynchronous pacing is generally safe, but it is not without the risks of losing AV synchrony. Also, pacing may rarely occur during the ventricular vulnerable period and may initiate ventricular arrhythmias.

XV. CARDIAC PACING: CLINICAL TRIALS

A. Conventional pacing trials

1. Numerous clinical trials, mostly small and nonrandomized, have been performed with regard to exercise capacity and quality of life for various pacemaker modes, chamber(s) paced, rate-adaptive pacing, and types of sensors.
2. Clinical trials have firmly established the superiority of rate-adaptive (VVIR) over fixed-rate ventricular pacing (VVI) with regard to quality of life and exercise performance.
3. Numerous clinical trials have been undertaken to prove the benefit of dual-chamber/atrial-based pacing in patients undergoing postoperative permanent pacemaker implantation for sinus node dysfunction or high-degree AV block.
4. There are conflicting data regarding the benefit of dual-chamber pacing over rate-adaptive ventricular pacing. Early nonrandomized trials demonstrated mortality benefit with DDD pacing over VVI in patients with complete heart block. However, in randomized prospective trials, atrial pacing has not been shown to decrease rates of death or heart failure in patients treated for sinus node

dysfunction and high-degree AV block. However, there are several randomized trials demonstrating that atrial-based pacing does, in fact, lead to a reduction in both atrial fibrillation and stroke. However, this benefit may be limited to patients with sinus node dysfunction. The one clear benefit that dual-chamber/atrial-based pacing provides is the avoidance of pacemaker syndrome, which can be seen in up to 10% of patients with VVI pacing.

5. The following paragraphs summarize some of the larger-scale, randomized studies of ventricular- versus atrial-based cardiac pacing modes.
 - a. **Pacemaker Selection in the Elderly (PASE) trial.** A single-blind, randomized, controlled trial of ventricular pacing versus dual-chamber pacing in 407 patients older than 65 years. The primary end point was quality of life with up to 30 months follow-up. Quality of life improved with pacemaker implantation. Patients with sinus node dysfunction, but not AV block, had significantly better quality of life with dual-chamber pacing than with ventricular pacing (2).
 - b. **Canadian Trial of Physiologic Pacing (CTOPP).** In this trial, 1,474 patients were assigned to ventricular pacing and 1,094 patients to physiologic pacing. During a mean follow-up period of 3 years, there was no significant effect on the risk of death, stroke, or hospitalization for CHF according to the type of pacemaker used. However, the annual rate of atrial fibrillation was significantly lower in the atrial pacing group, although there was a 2-year delay before this beneficial effect emerged. There was a 50% reduction in perioperative complications with the implant of ventricular pacing systems, but in the ventricular pacing group there was a 5% incidence of pacemaker syndrome that required upgrade to a dual-chamber device (3).
 - c. **Mode Selection Trial in Sinus Node Dysfunction (MOST).** A randomized trial that attempted to compare dual-chamber with single-chamber ventricular pacing in 2,010 patients with sinus node dysfunction. There was no advantage for dual-chamber pacing over single-chamber ventricular pacing in terms of the trial's primary end point: death from any cause or nonfatal stroke over 33.1 months of follow-up. However, some advantages were seen with the dual-chamber modality in secondary end points, including reductions in atrial fibrillation and symptoms of heart failure and improvement in quality of life (4). There was no difference in heart failure admission rates between the two groups.
 - d. **Pacemaker Atrial Tachycardia (Pac-A-Tach) trial.** This was a mode randomization study in 198 patients (median age 72 years), all of whom received dual-chamber rate-adaptive pacemakers programmed to either VVIR or DDDR pacing. Intention-to-treat analysis showed no significant difference in atrial tachyarrhythmia recurrence rates at 1 year (VVIR 43%; DDDR 48%; $p = 0.09$) (5).
 - e. **UK Pacing and Cardiovascular Events (UK PACE) trial.** This was a trial comparing VVI(R) and DDD pacing in 2,021 elderly patients (mean age 80 years) with high-grade AV block. Patients were randomized to DDD (50%), VVI (25%), and VVIR (25%). No difference was detected in rates of stroke, atrial fibrillation, or heart failure hospitalizations (6).
 - f. **Meta-analysis of trials comparing atrial- and ventricular-based pacing.** Healey et al. (5) in 2006 completed a large meta-analysis of all randomized controlled trials comparing ventricular- and atrial-based pacing modes. A total of 35,000 patient-years of follow-up were reviewed (7). There was no significant reduction in mortality or heart failure with atrial-based pacing. However, there was a significant reduction in atrial fibrillation (hazard ratio 0.80, 95% confidence interval [CI] 0.77 to 0.89) and a borderline reduction in stroke (hazard ratio 0.81, 95% CI 0.67 to 0.99).

6. The practice of RV apical pacing as the preferred method remains controversial. It provides a reliable and stable position for long-term ventricular pacing. However, RV pacing creates ventricular desynchronization and leads to several adverse effects, including LV systolic and diastolic dysfunction. Retrospective and prospective analysis has linked increased numbers of RV paced beats with increased incidence of atrial fibrillation and heart failure. Current forms of pacemaker technology that minimize RV pacing are preferred to older pacemaker technologies. The following are landmark trials that have associated RV pacing with deleterious outcomes.
 - a. **DAVID.** The DAVID trial was the first study of ventricular pacing strategies in implantable cardioverter–defibrillator patients. The trial hypothesized that dual-chamber pacing would result in a lower rate of heart failure in these patients with EF < 40% (8). At 1 year, rates of death and first hospitalization for heart failure were significantly increased in the dual-chamber group. The authors noted an increased rate of RV apex pacing in the DDD-70 group (60%) versus the VVI-40 group (3%). The authors concluded that the greater exposure to the deleterious effects of RV pacing in the DDD group led to worse outcomes.
 - b. **SAVE PACE.** This trial examined whether the application of newer technologies to limit frequency of ventricular pacing could lead to a decrease in atrial fibrillation in patients with dual-chamber pacemakers. Patients with sinus node disease, intact AV conduction, and a normal QRS interval were randomly assigned to receive conventional dual-chamber pacing or dual-chamber minimal ventricular pacing with the use of features to promote AV conduction and reduce ventricular dyssynchrony (9). Persistent atrial fibrillation was found to occur less frequently in the dual-chamber minimal ventricular pacing group (hazard ratio 0.60, 95% CI 0.41 to 0.88) than in the conventional dual-chamber group.
 - c. **Recommendations.** The most recent recommendations for cardiac pacing and resynchronization released by the AHA/ACC/HRS in 2008 specifically address the implications of apical versus RV outflow tract/septal pacing. The recommendations mention that small trials have demonstrated septal pacing preserved LV function over the mid- to long term and that His bundle pacing also appears to be beneficial. However, the guidelines note that it is too early to propose a recommendation concerning the optimal location of the RV pacing lead.

XVI. EVOLVING INDICATIONS FOR PACEMAKER THERAPY

A. Hypertrophic cardiomyopathy

1. **Presumed mechanism of benefit.** The idea of RV pacing to treat hypertrophic cardiomyopathy is based on the effective increase in left ventricular outflow tract (LVOT) diameter caused by altered septal activation.
2. **Recommendations.** Pacing is a class IIb recommendation in the 2008 ACC/AHA/HRS guidelines and is reserved for symptomatic drug-refractory patients with significant LVOT gradients who have contraindications for septal ablation or myectomy (see Table 54.2).

B. Long QT syndrome

1. **Presumed mechanism of benefit.** In patients with long QT syndrome, life-threatening episodes of polymorphic ventricular tachycardia and Torsades are typically preceded by pauses or severe bradycardia. By preventing these episodes, pacing may decrease the likelihood of events.
2. **Recommendations.** The 2008 ACC/AHA/HRS guidelines state that permanent pacing is reasonable for high-risk patients with congenital long QT syndrome.

XVII. FUTURE DIRECTIONS

- A. **Sensor technology.** Advances in physiologic sensors and rate adaptation algorithms include the following.
 1. **Multiple sensors for more physiologic pacing.** For example, a desirable sensor combination is an activity sensor, which typically has a more rapid response, and another sensor such as minute ventilation, which typically has a more delayed but workload-proportional response.
 2. **Sensor blending** refers to the relative contribution of each sensor during each phase of activity and may be programmable.
 3. **Sensor “cross-checking”** is done to determine if an increase in the intrinsic atrial rate is appropriate. If the sensor does not confirm activity while the pacemaker senses an increased atrial rate, the pacemaker will use the sensor to dictate the appropriate heart rate. Also, pacemakers with multiple sensors are able to detect intersensor disagreement and thereby avoid inappropriately rapid pacing due to a false-positive response of one sensor.

XVIII. GLOSSARY

A. Cardiac pacing: basic terminology

1. **“60,000 rule”.** Converts rate (bpm) to interval (milliseconds) and vice versa, as there are 60,000 milliseconds in 1 minute. Note the formula: $60,000 / \text{interval (milliseconds)} = \text{rate (bpm)}$.
2. **Anode.** Refers to the positive pole. The anode of a unipolar pacing system is the pulse generator case. The anode of a bipolar pacing system is the proximal ring electrode of the pacing lead.
3. **Capture.** The effective cardiac depolarization resulting from a pacing stimulus.
4. **Cardiac stimulation threshold (mA).** The minimal electrical energy required to consistently depolarize cardiac tissue through a given electrode. This threshold changes with time after implantation (acute, subacute, and chronic).
5. **Cathode.** Refers to the negative pole. The cathode of a unipolar pacing system is the electrode at the distal portion of the pacing lead. The cathode of a bipolar pacing system is the distal tip electrode of the pacing lead.
6. **Cross talk.** In dual-chamber pacing systems, the inappropriate detection (sensing) of an event or signal in one chamber by the sense amplifier of the other chamber (usually inhibition of a ventricular output pulse due to ventricular channel detection of an atrial output pulse).
7. **Current (I).** The rate of transfer or the flow of electricity, measured in milliamperes (mA).
8. **Elective replacement interval (ERI), also known as elective replacement time (ERT) or recommended replacement time.** Terms indicating the pulse generator has reached a point in its service life where system failure will likely occur within 3 to 6 months. The ERI indicator for a pacemaker varies between models and manufacturers, but is usually indicated by a change in pacing rate, mode, or function. Pacemaker manufacturers generally recommend pulse generator replacement when the ERI is identified. ERI/ERT indicators for various pacemaker models are published in a handbook that should be available in the pacemaker clinic.
9. **External EMI.** Electrical signals from noncardiac or nonphysiologic sources that may affect pacemaker function. Sources of EMI are discussed below.
10. **End of life.** Term indicating the depletion of battery power for the pulse generator. The EOL indicator for a pacemaker varies between models and manufacturers, but is usually indicated by a decrease in the magnet-related pacing rate to a certain percentage of the beginning-of-life rate. There may also be a change in pacemaker mode (e.g., from DDD to VVI). Telemetry of the

cell impedance of the pulse generator also provides information regarding the status of battery power for those pacemakers with such a feature. Pacemaker manufacturers generally recommend urgent pulse generator replacement if EOL of a device is identified. EOL indicators for various pacemaker models are published in a handbook that should be available in the pacemaker clinic.

11. **Fusion.** Results when the pacemaker output occurs at the same time as an intrinsic event, and both contribute to cardiac depolarization. The morphology of the fused beat has characteristics of both the paced and intrinsic events.
12. **Impedance (Z).** Total resistance to the flow of current through a conductor. For pacemaker systems, this includes resistance produced by electronic components and body tissues. Temporal changes in pacing impedance usually include a decreasing impedance over the first 1 to 2 weeks following implantation, then increasing impedance to a level that is somewhat higher than the impedance at the time of implantation. Serial measurements of pacing impedance may be useful for assessing lead integrity, as discussed later in this chapter.
13. **Magnet mode.** The response of a pacemaker when a magnetic field of sufficient strength is applied and closes the pulse generator's reed switch. The pulse generator paces at a predetermined rate and mode, which vary among pacemaker models and manufacturers. Generally, the mode is asynchronous pacing. Magnet mode can be used to assess pacemaker function and battery status (see discussion on ERI in Section XVIII.A.8 and on EOL in Section XVIII.A.10).
14. **Noncapture.** The absence of cardiac depolarization following a pacing stimulus.
15. **Ohm's law.** $V = I \times R$ (*voltage = current \times resistance*).
16. **Output.** The output of a pacemaker is determined by the voltage and pulse width.
17. **Oversensing.** The sensing of inappropriate cardiac or extracardiac signals and responding to them as if they were appropriate native sensed events. "Oversensing results in underpacing."
18. **Pacemaker-mediated tachycardia.** Sudden onset of a sustained ventricular paced rhythm at the maximum tracking rate of the pacemaker. PMT is sustained by continued active participation of the pacemaker in the tachycardia circuit. PMT is discussed in more detail in Section XIII.D.2.
19. **Pacing interval (milliseconds).** The interval between two consecutive paced events.
20. **Pseudofusion.** Results when an intrinsic event occurs before the pacemaker output is delivered. When this happens, the pacemaker output does not contribute to cardiac depolarization. The morphology of the pseudofusion beat resembles the intrinsic event.
21. **Pseudo-pseudofusion.** Results when a PVC that resembles the ventricular paced complex follows an atrial output spike.
22. **Pulse width.** The measurement in milliseconds of the pacemaker output spike (also known as pulse duration).
23. **Reed switch.** A switch within the pulse generator that closes when a magnetic field of sufficient strength is applied to it (such as a ring or donut magnet, or a programming head). The pacemaker will convert to magnet mode.
24. **Resistance (R).** The opposition to the flow of electrical current through a material, measured in ohms.
25. **Sensing.** The ability of a pacemaker to recognize native cardiac signals. Refers to the amplitude of the signal (mV) required for the pacemaker to detect the signal. Higher numbers reflect less sensitivity; lower numbers reflect more sensitivity.
26. **Undersensing.** The failure to recognize and respond appropriately to cardiac signals. "Undersensing results in overpacing."
27. **Voltage (V).** The difference in potential energy between two points, measured in mV.

B. Cardiac pacing: timing cycles and refractory periods

1. A = atrial-paced event.
2. Absolute refractory period: The period following a sensed or paced event during which the sense amplifier is unresponsive to incoming signals.
3. AEI = atrial escape interval: For atrial single-chamber pacing systems, the period from a sensed atrial event to the next atrial-paced event. For dual-chamber pacing systems, the period initiated by a ventricular sensed or paced event and ending with the next atrial-paced event.
4. ARP = atrial refractory period, which is the atrial timing cycle during which the atrial sense amplifier is unresponsive to incoming signals. For single-chamber atrial pacing modes, the atrial refractory period is initiated by an atrial sensed or paced event. For dual-chamber pacing modes, the AV interval and the PVARP determine the TARP. $TARP = AVI + PVARP$.
5. AV = atrioventricular sequential pacing.
6. AVI = atrioventricular pacing interval (also known as AV delay): In dual-chamber pacing, the period between an atrial sensed or paced event and a ventricular paced event (usually programmable).
7. Blanking period: An interval (usually 12 to 125 milliseconds) initiated by an output pulse during which the sense amplifier is temporarily disabled. In dual-chamber pacing, the blanking period is designed to prevent the inappropriate detection of signals from the other chamber (cross talk). For example, an atrial sensed or paced event initiates a ventricular blanking period during which the ventricular sense amplifier is temporarily disabled.
8. CDW = cross talk detection window: In dual-chamber pacing, a timing cycle (usually 51 to 150 milliseconds) immediately following the ventricular blanking period during which a ventricular sensed event is considered to be cross talk but results in a triggered ventricular output at the end of an abbreviated AV interval (safety pacing).
9. LRL = lower rate limit (also known as base rate or minimum rate): The rate at which the pacemaker paces in the absence of sensed intrinsic events (generally programmable in most pacemakers).
10. MSR = maximal sensor rate: A programmable value in rate-adaptive pacemaker systems that designates the highest pacing rate that can be achieved in response to a sensor input. The MSR may be programmed independently of the MTR.
11. MTR = maximal tracking rate (also known as upper rate limit, URL): A programmable value for dual-chamber pacemaker sensing and tracking modes that designates the highest ventricular pacing rate that can be achieved in response to atrial sensed events with 1:1 AV synchrony at the programmed AV delay.
12. P = native atrial depolarization.
13. R = native ventricular depolarization.
14. Relative refractory period: A “noise sampling” period following the absolute refractory period during which some incoming signals (generally those signals in the frequency range of interference) are monitored by the sense amplifier. Sensed signals during this period may result in the initiation of a new refractory period but do not reset the timing circuit.
15. RRAVD = rate-responsive atrioventricular delay. A programmable feature of some dual-chamber pacing systems that progressively shortens the PV or AV interval as the sinus or sensor-driven atrial rate increases. This is designed to provide a more physiologic AVI at higher heart rates and to allow tracking of higher atrial rates (a shorter AVI decreases the TARP), thereby lessening the chance of a fixed-block upper rate response.
16. V = ventricular paced event.

17. VRP = ventricular refractory period. The timing cycle initiated by a ventricular sensed or paced event during which the ventricular sense amplifier is unresponsive to incoming signals. This is not the same as the ventricular blanking period (see information regarding this in Section **XVIII.B.7**).

ACKNOWLEDGMENTS: *The author thanks Drs. Barbara Hesse, Matthew Hook, and Timothy Mahoney for their contributions to earlier editions of this chapter.*

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Antitachycardia Devices

I. INTRODUCTION

- A.** The modern implantable cardioverter-defibrillator (ICD) is a multifunctional, multiprogrammable electronic device designed to abort life-threatening arrhythmias. It is programmed to automatically detect and manage episodes of ventricular tachycardia (VT), ventricular fibrillation (VF), or bradycardia. Current ICDs are able to deliver multitiered therapies, which may include a combination of antitachycardia pacing (ATP), cardioversion, and defibrillation. The devices also offer bradycardic support, which may include rate-responsive single- or dual-chamber pacing and automatic mode switch function. Modern ICDs are able to deliver resynchronization therapy, a significant advancement in the management of heart failure. The devices are also able to store electrograms (EGMs), which can be easily retrieved. This function can be of immense use for follow-up management of the patient and programming of the device.

Multiple clinical trials have demonstrated the efficacy of ICDs to accurately detect and manage sudden cardiac death (SCD). The ICDs are superior to conventional therapy, with medications in both primary and secondary prophylaxis of SCD. The majority of patients who have indications for an ICD implant are those with left ventricular (LV) dysfunction, both ischemic and nonischemic.

- B.** Mirowski first introduced the concept of an ICD in the 1960s, with the first human implant reported in 1980. The early ICD implantations required a thoracotomy approach for placement of an epicardial lead system. Subsequent advancements in device and lead technology over the last 30 years have significantly reduced the size of the pulse generator, yet improved the programmability and diagnostic data stored within the device. An improved understanding of VF, defibrillation, and cardiac pacing has resulted in the development of biphasic shock waveforms and transvenous pace/defibrillation lead systems that preclude the need for epicardial patches. As a result, modern ICDs are more compact devices, with expansive programming capability placed by a transvenous approach. The newest generation of devices has the added capability of trans-telephonic interrogation.

II. ICD COMPONENTS

- A.** The current-day ICD is a sophisticated and intelligent computer. It consists of a generator and leads. The ICD generator consists of a battery, capacitors, DC–DC converter using an oscillator rectifier mechanism, a microprocessor, and telemetry communication coils and their connections. The generator serves as an active electrode within the shocking configuration in most of the modern ICDs and is thus called the “hot can.” The battery used in most of the ICDs is a lithium–silver vanadium oxide cell. This can generate approximately 3.2 V at full charge. Because most ICDs use two batteries connected in series, the full initial voltage is approximately 6.4 V. The generator has capacitors that can charge within 7 to 30 seconds to store up to 30 to 40 J of energy. This can be delivered to the heart within a 10- to 20-millisecond interval when therapy is required.

- B. The three essential functions of the ICD—**tachycardia detection, tachycardia therapy, and bradycardia pacing**—are delivered through the active electrodes, which are the noninsulated segments of the leads. Most of the current-day leads have sensing and pacing electrodes at the tip and a distal (right ventricle) and proximal (superior vena cava) shocking coil. The function of ventricular sensing and pacing is achieved by a technology similar to that in pacemakers. This is done through two “dedicated bipolar” electrodes at the distal end of the right ventricular (RV) lead (tip/ring). Sometimes, it may be achieved by “integrated bipolar” electrodes, wherein the bipole is formed by the tip of the ventricular lead and the distal shocking coil (tip/coil). Ventricular pacing in biventricular ICDs is from the tip of the RV and LV leads, respectively, to either the ring (true bipolar) or the distal shocking coil (integrated bipolar). The sensing could be from both RV and LV leads but could give rise to false tachycardia detection due to the problem of “double counting.” It is for this reason that the newer devices restrict the sensing function to the RV lead alone.
- C. For the delivery of shock therapy, most systems now incorporate a combined RV coil, superior vena cava coil, and active pulse generator can or sometimes a single RV coil with a hot can active pulse generator. Modern technology makes it feasible to incorporate all these electrodes and coils in a single lead implantable in a manner similar to a pacemaker.

III. INDICATIONS AND CONTRAINDICATIONS

- A. **ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities.** These are the most current guidelines for the implantation of ICDs. The guidelines stratify the various indications as class I, class II (a and b), and class III on the basis of the data from clinical trials and opinion of a panel of experts.
- B. **Class I indications.** These are clinical situations or conditions for which there is evidence and/or general agreement that ICDs are useful and effective.
- (1) Survivors of SCD secondary to VF or hemodynamically unstable VT
 - (2) Syncope of unknown etiology with inducible VF or hemodynamically significant VT during electrophysiology study
 - (3) Structural heart disease and spontaneous hemodynamically unstable or stable VT
 - (4) Ischemic cardiomyopathy, New York Heart Association (NYHA) class I, and a left ventricular ejection fraction (LVEF) $\leq 30\%$ who are at least 40 days post myocardial infarction (MI)
 - (5) Ischemic cardiomyopathy, NYHA class II or III with an LVEF $\leq 35\%$ who are at least 40 days post-MI
 - (6) Ischemic cardiomyopathy, ejection fraction (EF) $\leq 40\%$, nonsustained ventricular tachycardia, and inducible VF or sustained VT at electrophysiology study
- Nonischemic cardiomyopathy, NYHA class II or III, and LVEF $\leq 35\%$.
- C. **Class IIa indications.** These are conditions for which there is conflicting evidence about the usefulness of ICD therapy, with the weight of evidence/opinion in favor of usefulness/efficacy.
1. Unexplained syncope with significant LV dysfunction and nonischemic cardiomyopathy
 2. Normal or nearly normal LVEF with sustained VT
 3. Patients with hypertrophic cardiomyopathy and at least one risk factor for SCD
 4. Patients with arrhythmogenic RV dysplasia with at least one risk factor for SCD
 5. Patients with long QT with syncope or VT while taking β -blockers
 6. Patients waiting heart transplantation (nonhospitalized)
 7. Patients with Brugada with a history of syncope or VT but no episodes of cardiac arrest
 8. Patients with catecholaminergic polymorphic VT with syncope or sustained VT while taking β -blockers
 9. Patients with cardiac sarcoid, giant cell myocarditis, or Chagas disease.

- D. Class IIB** (usefulness/efficacy is less well established by evidence/opinion)
1. Nonischemic cardiomyopathy with an EF \leq 35% and NYHA class I
 2. Long QT and risk factors for SCD
 3. LV noncompaction patients
 4. Patients with familial cardiomyopathy and a predisposition to SCD
 5. Patients with structural heart disease and syncope but with no identifiable etiology
- E. Class III indications/contraindications.** These are conditions for which there is a general agreement that ICDs are not useful and possibly harmful. These include patients with a structurally normal heart and syncope without any inducible ventricular arrhythmias. ICDs should also be avoided in patients with VT and a treatable/ablatable cause (Wolff-Parkinson-White syndrome, outflow tract VTs, fascicular VTs, etc.) or a reversible cause (acute MI, myocardial ischemia, electrolyte imbalance, drug toxicity, or trauma). It is also important to avoid using ICDs in patients with severe psychiatric illnesses or in patients with terminal illnesses, where the expected life span is less than 12 months. ICDs could do more harm than good in patients with incessant ventricular arrhythmias, where it is important to control the arrhythmia before ICD implantation to avoid recurrent painful shocks. ICDs are also contraindicated in patients with NYHA class IV heart failure that are drug refractory and are not candidates for heart transplantation or cardiac resynchronization therapy (CRT).

IV. IMPLANTATION

- A. Device implantation.** Currently, available devices are small enough to allow implantation in the left pectoral region. Animal studies have shown that the defibrillation efficacy of the hot-can ICDs is superior in the left pectoral or axillary regions followed by the right pectoral and then the abdominal sites. A right pectoral system may be necessary in patients who have vascular access problems on the left side or who have undergone pectoral surgery (e.g., mastectomy). For patients with high defibrillation thresholds (DFTs), additional lead placement, such as a subcutaneous array/coil, an azygous coil, a coronary sinus coil, or an epicardial patch, may be necessary. Epicardial patch placement is usually reserved for patients who have failed to meet implantation criteria with a transvenous lead system or if there has been previous bilateral pectoral or tricuspid valve replacement surgery.

For pectoral implants, a single 2" to 3" incision is made transversely below the clavicle, about 1 cm below and parallel to the deltopectoral groove. Transvenous lead placement is achieved through a subclavian vein puncture or by cephalic vein cutdown. An "extrathoracic" subclavian vein puncture or cephalic vein cutdown for access minimizes the risk of pneumothorax and also the risk of lead failure due to subclavian crush injury.

- B. Lead placement.** The lead is advanced to the RV apex under fluoroscopic guidance, where the tip is secured via an active fixation screw or embedded in the trabeculae with passive fixation tines. It is important to assess the quality of signals at the time of implant, as it is the best guide to the adequacy of long-term sensing of the lead. The DFT is optimized with the lead placed at the RV apex; therefore, this position is often preferred even if there is compromise of the sensing thresholds. If there is already a pacemaker lead in the RV apex, then septal placement of the lead tip is chosen so that the lead tips are at maximal distance from each other to avoid device-device interactions. On occasion, placing an additional pacing-sensing lead in the right ventricle may be necessary when the defibrillation efficacy and pace-sense function of the leads are optimized at different locations.
- C. Threshold studies.** The lead is tested for pace-sense thresholds using an external high-voltage system analyzer or pacing system analyzer. In general, an acute pacing threshold of 2 V or less, R-wave amplitude of 5 mV or more, and lead impedance within the accepted range of the manufacturer (typically 300 to 1,200 Ω) are

necessary to meet the implant criteria. The lead is secured within the pocket with a suture sleeve tie-down. If the device uses an atrial and/or an LV lead, then these are implanted at this time. The leads are attached to the pulse generator and the system is placed in either a submuscular or a subcutaneous pocket. The pulse generator should be placed with excess lead coiled posteriorly to reduce the risk of damaging the leads at the time of generator change and to maximize the ability to communicate with an external programming wand. The device is then interrogated to assure appropriate communication. Pace-sense thresholds are again tested by telemetry to demonstrate consistency.

- D.** Defibrillation testing is best assessed by evaluating the DFT, which is defined as the lowest delivered shock strength required for successful defibrillation. A synchronized sinus test shock may be performed by delivery of a low-energy (<2 J) synchronized shock delivered on the QRS complex. This low-energy test allows the assessment of sensing as well as shock impedance (typically 35 to 90 Ω). For the purpose of defibrillation testing, VF is typically induced with a shock on T wave. Alternatively, or if shock on the T wave is unsuccessful, ultrafast burst pacing (30-millisecond intervals) or application of an alternating current may be used. Appropriate ICD detection and effective therapy are verified. In our lab, we typically start with a 10 to 15 J therapy, with subsequent therapies escalating in steps of 5 to 15 J. Usually a maximum of three device-based therapies are attempted before rescue with external defibrillation at maximum energy. Two successful therapies that are at least 10 J less than the maximal output of the device are generally required. In general, this approach identifies the level of energy required to achieve a 50% to 75% success rate of defibrillation. Defibrillation therapy is then programmed at a level at least 10 J over the DFT. Rarely, a patient may require the addition of a shocking coil in the superior vena cava, subcutaneous patch, or subcutaneous array to achieve an adequate safety margin.
- E. Risks and complications.** The risks involved with implantation are similar to those of pacemaker insertion. Operative risks include bleeding, pneumothorax, hemothorax, infection, myocardial damage, vascular/cardiac perforation, tamponade, thromboemboli, deep venous thrombosis, acceleration of arrhythmias, air embolism, and death. A rare but dangerous complication is the occurrence of electromechanical dissociation or refractory VF during DFT testing. Due to the nature of the procedure, a separate standby external pacemaker-defibrillator should be immediately available for rescue therapy should the implanted device fail to appropriately treat an arrhythmia. The overall mortality rate is much less than 1%. Late complications include chronic nerve damage, erosion, extrusion, fluid accumulation, infection, formation of hematomas/cysts, keloids, lead migration, lead dislodgment, and venous occlusion.

V. DEVICE REPLACEMENT

- A.** Battery status is determined by the measured voltage and this is retrieved with device interrogation. Generator replacement is generally recommended when the device reaches a battery voltage of around 2.6 V, termed elective replacement indicator. In such situations, the generator should be replaced within a few months. With continued depletion of the battery voltage, the generator reaches end of life, a situation that indicates a more urgent need for generator replacement as the battery voltage drops below 2.2 V. This may lead to longer charge times and incomplete or inappropriate function of the device.
- B.** Pulse generator replacement represents a vulnerable period for the ICD/lead system. A fourfold increased risk of infection has been reported with ICD pulse generator replacement. In the past, manufacturers have had multiple-lead models of variable pin lengths and diameters. Beginning in 1991, they adopted the 3.2-mm international pace-sense standard (IS-1) and the 3.2-mm defibrillation standard (DF-1). Prior to an attempted device replacement, assessment of the lead model should be done to verify that the appropriate replacement header or adapters are available at the time of surgery.

- C. Leads may be inadvertently damaged during exploration of the pocket or during the exchange of pulse generators. Intraoperative assessment of lead function is imperative prior to introducing the replacement generator to the operative field. Replacement of a pace-sense or defibrillation lead may be necessary and requires the use of a different device header.

VI. TACHYCARDIA DETECTION AND THERAPY

- A. **EGM and tachycardia sensing.** The ICD senses the intracardiac EGM signal via the implanted ventricular sensing electrodes. Recognition of a ventricular arrhythmia mainly depends on the analysis of the R-R intervals (heart rate is determined similarly). Accuracy of the EGMs depends on the health of the adjacent myocardium and appropriate contact. Accuracy also depends on far-field signals from the muscles, atrium, or other sources of electromagnetic interference. The sensed signals are passed through a band-pass filter that consists of high- and low-frequency cutoffs to represent true signal events. The accuracy of the signals in the newer devices has been further improved by analysis of the signal frequency, slew rate, amplitude, EGM width, autogain, and autothreshold. These variables are important in helping the device to differentiate VT and VF from other events like atrial fibrillation, sinus tachycardia, and other supraventricular tachycardias, thus reducing the incidence of spurious shocks.

Each EGM event and R-R interval is marked and detected, and there are various algorithms that attempt to identify the events as either normal or abnormal. The “abnormal” includes bradycardia that requires pacing, VT requiring ATP or low-energy synchronized shocks, or VF requiring defibrillation. Most of the algorithms depend on the ventricular rate criterion. Other variables, such as the suddenness of onset, variation in cycle length, and change in EGM morphology, help to increase the specificity for diagnosis but at some cost of reduced sensitivity. These should be adjusted and programmed based on the individual requirement and clinical scenario for every patient.

- B. **Event detection** occurs if the device reaches a specified number of intervals programmed by the physician to detect VT or VF, at which point the ICD delivers the prescribed therapy. Most of the devices reconfirm the ongoing episode to avoid therapy for nonsustained events. After delivery of therapy, the device either confirms termination of the episode or meets criteria for redetection, and the next programmed therapy is delivered. The ICD automatically adjusts its sensitivity thresholds following sensed and paced events through an autogain mechanism. This allows the device to automatically adjust its sensitivity during a tachycardia episode in response to the changing amplitude of the ventricular signal.
- C. **Atrioventricular (AV) sequential devices** incorporate programmable dual-chamber supraventricular criteria to exclude management of supraventricular tachyarrhythmias from inappropriate detection of VT or to identify concurrent VT and supraventricular tachycardia. Biventricular devices could pose problems of double counting and unnecessary therapies in patients with the older biventricular devices, where the sensed input is from both the RV and LV leads. The use of newer devices that have sensing inputs from only the RV leads should limit this problem. An additional feature of these devices is the capability to individually program the pacing output and timing of the RV and LV leads through separate ports.
- D. **Tachycardia therapy.** Most devices allow for programming of several tachycardia zones. The VT zone is programmed with a lower detection cutoff that would include any clinical VT events. Ideally, the cutoff rate for the detection of tachycardia should be above the patient's maximal heart rate to avoid therapy for sinus tachycardia. ATP schemes include burst pacing and ramp pacing. Burst pacing sequences deliver a set of ventricular pulses at a fixed rate faster than that of the VT in an attempt to terminate the reentry VT by overdriving the circuit. Ramp pacing consists of a set of ventricular pulses in which each subsequent paced interval is incrementally shorter

than the preceding one. Although this is a more aggressive protocol, there is also a higher chance for the VT degenerating into VF with this therapy. Overall, some studies have shown about 90% success in termination of VT with ATP.

Following a failed ATP attempt, interburst decrement allows a more aggressive shortening of the intervals during either a burst or a ramp attempt. The first pulse of a burst or ramp sequence (S_1) is delivered at a calculated percentage of the tachycardia cycle length. The S_1 percentage cycle lengths, number of pulses, interburst decrement, and number of ATP attempts are all programmable features. In addition, cardioversion therapy (1 to 36 J) can be programmed in a VT zone. All VT zones have a programmable time limit on episode duration at which point the device defaults to the next zone. Also, if a tachycardia is accelerated to a faster arrhythmia, then the ICD will deliver the therapy appropriate for the rate of the accelerated tachycardia.

- E. Defibrillation therapy.** Successful ICD management of VF can only occur with defibrillation therapy. All devices are programmed with a VF zone due to the risk of acceleration with ATP or cardioversion. Because of the hemodynamic instability seen with fast VT or VF, most devices are typically programmed to manage any sustained episode with rates higher than 180 to 200 beats/min with defibrillation therapy. The device should be programmed with at least a 10-J safety margin over the DFT observed either at implant or during follow-up testing. Up to six additional shocks may be programmed, with maximal outputs programmed at the second or third shock and onward.

VII. BRADYCARDIA DETECTION AND THERAPY

- A.** All currently available ICDs provide basic VVI pacing with separate programmable post-shock lower rate limit and output. Some dual-chamber devices have been introduced with an atrial lead for diagnostic use only or for AV-synchronized pacing. These devices allow multiple programmable pacing modes, including single- and dual-chamber, fixed-rate, or rate-responsive pacing with automatic mode switch. These expanded pacing modes have obviated the need for a separate dual-chamber pacemaker. In addition, they may reduce the inappropriate shocks attributed to supraventricular tachycardia. Such devices may also have capabilities to detect and treat atrial arrhythmias in a manner similar to that for the ventricular arrhythmias. However, in patients without any pacing indications, it may actually be detrimental to pace the right ventricle, especially in patients with preexisting LV dysfunction. This has been well demonstrated in the Dual Chamber and VVI Implantable Defibrillator (DAVID) trial. Such patients should either be given a single-chamber ICD or, if there are indications for a dual-chamber ICD for tachycardia discrimination or atrial arrhythmias, be programmed for backup pacing in the VVI mode.
- B.** In AV-synchronized devices, the ICD can continue to sense tachyarrhythmias in both chambers regardless of the programmed bradycardic pacing mode. To maintain proper sensing, both atrial and ventricular sensing thresholds are adjusted with autogain. The ICD has multiple blanking periods to avoid post-pacing polarization, T-wave oversensing, and cross talk between chambers. To avoid undersensing of tachyarrhythmias, short cross-chamber blanking periods after paced events and no cross-chamber blanking after sensed events are necessary. The AV synchronous devices have programmable refractory periods available for bradycardia functions, but these refractory periods do not affect tachyarrhythmia detection.

VIII. MAGNET FUNCTION

- A.** Confusion abounds concerning the function of a magnet with ICDs. The pulse generator contains a reed switch that is closed when a magnet is placed over the device. Closure of the reed switch prevents delivery of tachyarrhythmia therapy. Unlike pacemakers, bradycardia pacing is not affected by the use of a magnet in ICDs. Normal device therapy resumes when the magnet is removed and the reed switch opens.

IX. DEVICE–DEVICE INTERACTION

- A. Device–device interaction remains a significant issue when multiple-lead systems or devices are used. When a new lead is placed, the lead should be positioned as far from the other leads as possible (at least 2 cm). A dedicated bipolar sensing lead is preferred to minimize the potential of far-field oversensing of the alternate pacing lead.
- B. During the implantation procedure, the devices should be tested for device–device interaction. To simulate a worst-case scenario, the pacemaker is programmed in a unipolar configuration at high output. The real-time ICD EGM and marker channels are observed for oversensing of the pacemaker output, resulting in double counting of the paced QRS complex. This may lead to an inappropriate ICD discharge. Defibrillation testing is performed with the pacemaker programmed to DOO/VOO at high output to verify appropriate VF detection and therapy. Pacing stimuli may lead to ICD undersensing of VT/VF, with interpretation of the pacing artifact as “sinus rhythm” and failure to recognize the underlying arrhythmia. In addition, the ICD may affect the pacemaker by resetting the pacemaker pulse generator with a high-voltage shock. The pacemaker is programmed with the sensor “on” during an ICD high-output defibrillation test. The pacemaker is subsequently interrogated to verify appropriate communication and programmed mode. Whenever multiple devices are present and inappropriate ICD discharges are suspected, electrophysiology lab testing for device–device interaction is warranted. Device–device interaction should also be considered when a patient presents with resetting of the programmed mode, output configuration, or failure of communication with the device.

X. MANAGING AND FOLLOWING PATIENTS

- A. In the United States, the government mandates patient registration and tracking. Once registered, a patient receives a permanent identification card to carry at all times. A MedicAlert is strongly encouraged. Manufacturer guidelines suggest that patients should follow up every 1 to 4 months depending on clinical status. Even if trans-telephonic follow-up is available, it should be supplemented by clinic visits. Patients should be informed that they are likely to receive therapies. At the follow-up visit, a history of symptoms that might suggest tachyarrhythmias should be obtained. The diagnostic and episode data should be reviewed. Current devices also include stored-episode EGMs to allow review of aborted shocks as well as delivered therapies. Device pacing and sensing thresholds should be obtained. There are no specific guidelines for follow-up testing of ICD defibrillation function. In general, patients experiencing device activation should be evaluated shortly after the event to assess for safe and appropriate device function. When device function or concomitant antiarrhythmic therapy is modified, an evaluation of the sensing, pacing, and defibrillation thresholds is often necessary. Practice patterns vary widely regarding empirical device programming and electrophysiologic testing of modified ICD programming. Some sources recommend that operating a motor vehicle should be avoided for 6 months following a symptomatic arrhythmic event.
- B. In general, ICD pulse generators have a 4 to 6 year longevity depending on usage. The programmer allows evaluation of battery status. As the device approaches the elective replacement interval, follow-up visits should be intensified. In general, once the device reaches the elective replacement interval, it operates normally for at least 3 months depending on the frequency of therapy. Capacitor deformation occurs during periods when no shocks are delivered and results in longer charge times as well as decreased battery longevity. Current ICDs perform an automatic capacitor reformation that charges the capacitors and delivers the energy to an internal test load. This function improves subsequent charge times and battery longevity. Capacitor reformations should be conducted manually every 3 to 6 months if not conducted automatically.

- C. Typically, 40% of patients receive a therapy within the first year after implantation and 10% per year thereafter. If multiple ICD discharges are experienced, medical attention should be sought emergently. **Failure to discriminate between ventricular and supraventricular rhythms is the most common reason for inappropriate shocks.** It is important to evaluate the patients for appropriateness of therapy. The most common cause of inappropriate shocks is atrial fibrillation with a fast ventricular rate. Shocks delivered during physical exertion noted to have gradually increasing heart rates and gradually decreasing V-V intervals suggest sinus tachycardia. Therapy is likely to be inappropriate in this setting also. Ideally, the cutoff rate for the detection of tachyarrhythmias should be greater than the patient's maximal heart rate. In many cases, the VT rate falls within the patient's achievable sinus rate. Programmable enhancements, such as sudden onset and sustained high rate, can allow sinus tachycardia overlap into the VT zone without delivery of an inappropriate shock. Additional enhancements such as morphology discrimination of the ventricular EGM as well as the introduction of dual-chamber devices with timing intervals, marker channels, and mode-switching capabilities are likely to improve the specificity of device therapy.
- D. In the event of multiple ICD discharges, a magnet can be used to inhibit ICD therapy so that the underlying rhythm can be appropriately assessed and managed. The device should be interrogated as soon as possible to assess ICD function and facilitate diagnosis. If a supraventricular tachycardia is present, then it should be managed as medically appropriate. For patient comfort, the magnet should be left in place to inhibit ICD therapy until the device can be reprogrammed or the supraventricular tachycardia is terminated. If VF is present, the device is assumed inoperable and cardiopulmonary resuscitation with external defibrillation should be applied.
- E. Patients receiving ICDs may suffer from significant psychological and emotional disturbances. Education and psychological support are beneficial in improving these patients' quality of life.

XI. ELECTROMAGNETIC INTERFERENCE. Patients should be counseled to avoid sources of electromagnetic interference because such interference may cause the pulse generator to become inhibited and either fail to deliver appropriate therapy or deliver inappropriate therapy. Potential sources of electromagnetic interference include industrial transformers, radiofrequency transmitters such as radar, therapeutic diathermy equipment, arc welding equipment, toy radio transmitters, antitheft devices, and magnetic security wands. The safe use of medical technologies such as electrosurgery, lithotripsy, external defibrillation, and ionizing irradiation can be accomplished by deactivating the device before the event. Shielding of the device is also appropriate when possible. The device should be evaluated for appropriate operation following exposure. Magnetic resonance imaging is contraindicated. Reports of interference created by cellular phones may be related to either a magnetic field from within the phone or the radiofrequency signal generated by the phone. It is suggested that if a patient with ICD wishes to use a cellular phone, it should be held to the ear opposite the device and carried at least 6" to 12" from the pulse generator; in addition, the phone should not be carried in a pocket close to the device.

XII. FUTURE. ICD implantation rates have risen tremendously over the last two decades and are expected to rise further with evolving therapies and indications. Multiple clinical studies have demonstrated the role of ICDs in the primary and secondary prevention of SCD. Multiple trials have also demonstrated the role of an ICD in combination with CRT in reducing mortality and hospital admissions in patients with heart failure. Improvements in electronic technology will continue to expand programming capabilities of these devices while reducing their size. ICD lead technology is also expected to improve, thereby decreasing the number of lead-related complications. Leadless systems are in clinical trials and may be an option for select patients in the future.

SUGGESTED READING

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Cardiac Resynchronization Therapy

I. INTRODUCTION. The prevalence of heart failure (HF) in the United States has increased considerably in the past two decades as a result of the aging population and better medical management of left ventricular dysfunction (LVD). Unfortunately, medical therapy is not completely effective in preventing or reversing the progression of HF, and as a result, patients with advanced HF have limited options. A subset of patients with systolic LVD who have associated ventricular conduction delay are at highest risk for HF progression and a poor overall outcome. Since the late 1970s, various investigators have shown that left bundle branch block (LBBB), right ventricular (RV) pacing, or intraventricular conduction delay (IVCD) is associated with a less favorable hemodynamic profile in those with LVD and even in normal subjects. **The mechanism for this phenomenon is thought to be due to asynchronous and inefficient contraction of opposing areas of the ventricular myocardium. More importantly, restoring synchronization, either via simultaneous pacing of the RV apex and the left ventricular (LV) free wall or with timed LV free wall activation, can lead to a significant hemodynamic improvement.** In 1994, two investigators in Europe applied cardiac resynchronization therapy (CRT) in the clinical setting for the first time. Subsequent small observational studies suggested benefit from synchronous pacing. Larger randomized clinical trials confirmed these findings. CRT was first approved for maximally medically managed patients with persistent New York Heart Association (NYHA) class III or IV HF symptoms due to severe LVD associated with prolonged QRS duration. Further randomized studies, powered for mortality, showed a significant survival benefit with CRT or the combination of CRT with a defibrillator (CRT-D). More recently, CRT has been shown to be beneficial in less symptomatic patients. Unfortunately, not all patients who are selected for CRT based on current guidelines respond. Furthermore, some patients who would not be selected for CRT based on the current guidelines may actually benefit from this therapy. One of the major current challenges in this field is the optimal definition of the appropriate and cost-effective use of this expensive technology.

II. MECHANISM OF LV DYSSYNCHRONY. The normal pattern of electrical activation of the ventricular myocardium, once the impulse passes through the atrioventricular (AV) node, starts in the His bundle, followed by simultaneous activation of the right and left bundles of the Purkinje system and then by myocardial depolarization. The Purkinje system is electrically isolated from the rest of the myocardium until it reaches its exit points at the Purkinje–myocardial junctions. As a result, typical LV myocardial activation occurs from the apex to base, simultaneously in the septum and in the LV free wall, and is described as synchronous. Due to tight electromechanical coupling of the myocardium, synchronous ventricular activation is followed by synchronous ventricular contraction.

In the setting of conduction delay, the electromechanical coupling of the heart is disrupted, leading to dyssynchrony. Over time, electromechanical uncoupling leads to impaired stroke volume, worsened mitral insufficiency, prolonged LV isovolumetric

events, and impaired diastolic filling. These effects contribute to adverse remodeling in the already impaired heart, creating a vicious cycle that perpetuates this process into more advanced HF. As a result, when comparing patients with similar degrees of LVD, **those with conduction delay have a worse overall prognosis**. CRT has been shown to reverse this deleterious process. Synchronized pacing has been shown to improve LV function without increasing oxygen demand, suggesting that the improvement is related to better efficiency of the LV chamber.

Interestingly, dyssynchronous activation and contraction have an undesirable effect in patients **without** LV systolic dysfunction also. When compared with normal controls, patients with LBBB have a lower ejection fraction (EF), are more likely to develop HF, and have a tenfold greater cardiovascular morbidity and mortality risk. In some patients (patients with chronic LBBB, frequent premature ventricular contractions, or chronic RV pacing), the conduction delay in and of itself may cause deterioration in the EF. In this population, treatment with CRT can have profound effects potentially normalizing the LV function.

III. TYPES OF DYSSYNCHRONY

- A. **AV dyssynchrony.** In the setting of PR or QRS prolongation, the atrial contribution to LV filling is abnormal. Atrial systole occurs too early with respect to ventricular diastole, leading to early truncation of passive LV filling. Early atrial systole also causes an early rise in diastolic ventricular pressure, leading to diastolic mitral regurgitation (MR). Compromised LV filling and MR cause lower cardiac output. AV synchronization can improve cardiac output in HF by as much as 20%.
- B. **Interventricular dyssynchrony.** Early RV activation present during LBBB, IVCD, or RV pacing leads to early RV contraction, creating a pressure gradient between the RV and LV that negatively affects LV filling, which translates to a decrease in LV preload and a subsequent decrease in cardiac output. In the early development of CRT, interventricular dyssynchrony was thought to be a major contributor to adverse events in patients with HF and conduction disease. More recently, however, interventricular resynchronization has not been shown to be of significant benefit, clinically calling the role of interventricular dyssynchrony in the failing heart into question.
- C. **Intraventricular dyssynchrony.** In the presence of conduction delay, there is a substantial delay in the activation of certain LV segments compared with others, leading to an inefficient back-and-forth mechanical interaction that results in inefficient myocardial contraction. In the case of a native LBBB for example, there is a significant delay in activation between the early activated septum and the late activated posterolateral wall, often resulting in profound delays between segments. **Mitigation of intraventricular dyssynchrony** is currently thought to be the primary mechanism of improved myocardial performance with CRT.

IV. ASSESSMENT OF DYSSYNCHRONY (see Table 56.1). While CRT has been established as an effective therapy for patients with conduction delay and LVD, approximately 30% of patients meeting current implantation criteria fail to respond (depending on one's definition of response). This has spawned a major research effort to identify dyssynchronous contraction preimplantation to refine appropriate patient selection for this procedure. In addition to the three varieties of dyssynchrony already discussed, dyssynchrony can also be broken into "mechanical" and "electrical." Electrical dyssynchrony refers to delays in depolarization from one segment to another, whereas mechanical dyssynchrony refers to contraction delays from one segment to another. While the two are presumed to be closely linked, **current measures of electrical and mechanical dyssynchrony have often shown poor agreement**. For example, almost all clinical trials have used prolonged QRS duration, a crude marker of electrical dyssynchrony, as a requisite for inclusion. The relationship, however, between QRS duration and various

TABLE 56.1 Commonly Used Echocardiographic Measurements of Dyssynchrony

Method	Measurement	Value (milliseconds)
M-mode	Septal to posterior wall delay	> 130
Pulsed tissue Doppler	Opposing wall delay onset velocity	> 60
Color tissue Doppler	Opposing wall delay peak velocity	> 65
Color tissue Doppler	12-Segment standard deviation	> 34
Tissue Doppler radial strain	Septal to posterior wall delay	> 130
Tissue speckle tracking radial strain	Septal to posterior wall delay	> 130
Three-dimensional echocardiography	12-Segment standard deviation	> 36

measures of mechanical dyssynchrony has been poor. Studies have revealed that up to 30% of patients with a prolonged QRS duration do not have mechanical dyssynchrony as assessed by magnetic resonance imaging (MRI) or echocardiography, whereas up to 30% of patients with a normal QRS duration and symptomatic HF have evidence of mechanical dyssynchrony on echo or MRI and could potentially benefit from resynchronization therapy. Currently, the development of new measures of both electrical and mechanical dyssynchrony is an area of intense research. While newer, noninvasive measures of electrical dyssynchrony other than the QRS duration are on the horizon, currently, the bulk of research on dyssynchrony has been dominated by the various metrics of mechanical dyssynchrony, mostly using various echocardiographic techniques.

A. Echocardiographic assessment of dyssynchrony. The assessment of cardiac mechanical dyssynchrony was initially made with M-mode and pulsed-wave Doppler. Subsequently, tissue Doppler imaging (TDI) and tissue synchronization imaging have been used. More recently, three-dimensional echocardiography and speckle tracking technology have shown considerable promise. The main difficulty with all measures of mechanical dyssynchrony has been reproducibility across centers. In the large, multicenter PROSPECT trial, multiple echocardiographic measures of mechanical dyssynchrony were tested. **None, however, were found to be both a sensitive and a specific predictor of subsequent response to CRT.** Technical and interpretative variability across centers was thought to be a major reason behind the only modest predictive ability.

- 1. Pulsed-wave Doppler** has been used to assess interventricular dyssynchrony by measuring the time delay between initiation of RV and LV ejection, known as the presystolic ejection period. One advantage of this technique is good feasibility and reproducibility. While values > 40 milliseconds are considered to be abnormal, the clinical utility of this measure remains to be proven.
- 2. Septal to posterior wall motion delay** as assessed by **M-mode** in the parasternal long or short axis view has been used to detect intraventricular dyssynchrony. A value > 130 milliseconds has been associated with a greater response to CRT in terms of symptomatic improvement, LV remodeling, and EF increase. Advantages include the ability to perform this measure on all echocardiographic systems without the requirement of specialized software. Unfortunately, this parameter has significant limitations. It evaluates dyssynchrony in only two segments of the myocardium: the septum and the posterior wall. Additionally, it may be difficult to obtain in up to 40% of patients due to poor acoustic windows

as one must be perpendicular to the myocardial walls, which is often difficult in patients with low parasternal windows.

3. **Tissue Doppler imaging.** This technique uses pulsed-wave Doppler to record myocardial velocities at the basal septum and the basal lateral wall as close as possible to the mitral valve annulus in the four-chamber view. Time from the onset of the QRS to the onset of systolic velocity or to the peak of systolic velocity is measured. So too is the difference in these measurements between the septum and the lateral wall. Values > 62 milliseconds for time to systolic velocity initiation and 65 milliseconds for time to peak systolic velocity are abnormal and have predicted a favorable clinical and echocardiographic response to CRT. TDI has excellent temporal resolution and does not require endocardial border identification for determining the degree of delay. The limitations of TDI are as follows: (1) occasional difficulty in identifying the true peak of systolic velocity and (2) because segments are not assessed simultaneously, heart rate variability and respiration can lead to false comparisons. To better deal with these limitations, computer software has been developed that allows postprocessing of Doppler data so that all of these measurements are determined from one image. Additional views (apical three-chamber and apical two-chamber) may be used to increase the number of myocardial segments assessed. This technique improves both specificity and sensitivity in the identification of mechanical dyssynchrony, as compared with older, less sophisticated methods.

Another major problem with current methods of TDI is that they assess systolic motion only in the longitudinal plane of the heart and, therefore, may be prone to artifact from tethering and pulling. The heart contracts in three different planes: longitudinal, radial, and rotational. The latter two are not assessed by conventional TDI but have a greater contribution to ventricular contraction than the longitudinal plane.

4. **Three-dimensional imaging.** The development of three-dimensional echocardiographic technology now allows the measurement of endocardial wall motion in reference to a center point. Using computer assistance, the endocardial border is tracked. Only the end-systolic and end-diastolic positions of the ventricular apex and mitral annulus must be determined by the operator. This technique permits the calculation of the three-dimensional dyssynchrony index, which quantifies mechanical dyssynchrony as the standard deviation of the time to minimum systolic volume as a percentage of the cardiac cycle length. While three-dimensional motion delay imaging has shown promise as predictive of subsequent reverse remodeling following CRT, it remains limited by the need for good image quality and a stable heart rhythm.
- B. New echocardiographic indices of mechanical dyssynchrony.** Newer echocardiographic techniques focus on eliminating the shortcomings of longitudinal TDI, namely, the tethering and pulling artifact, and lack of radial and rotational strain assessment.
1. **Strain imaging** performed in the four-chamber and parasternal short axis views incorporates velocity sampling in two nearby points. The sampled velocity difference divided by the separation distance is proportional to strain rate, which when integrated over time can provide the strain value. Strain, unlike velocity, does not depend on tethering or pulling of the myocardium. The major limitation of this technique is that it is time consuming and requires extensive off-line postprocessing.
 2. **Speckle tracking.** Speckle tracking relies on the automated tracking of unique acoustic backscatter during standard grayscale imaging. Both strain and its planar dimensions may be assessed using semiautomated off-line analysis, which improves reproducibility and feasibility. This technique is promising and is currently being used as a measure of mechanical dyssynchrony in ongoing clinical trials.

C. Alternative modalities for dyssynchrony assessment. Tagged MRI is ideal for measuring strain; however, due to its high cost, high level of complexity, and contraindications in patients with pacemakers or implantable cardioverter-defibrillators (ICDs), it is of limited use with respect to dyssynchrony assessment.

V. ROLE OF CRT. The primary role of CRT is **to improve systolic and diastolic LV performance via an improvement in chamber efficiency**, thereby leading to symptomatic improvements in patients with medication refractory HF. The **systolic improvement** is usually noticed **within a week** of device implantation. In clinical trials, the **EF improved by an average of about 5%** with a significant improvement in MR and was accompanied by symptomatic improvement, as evidenced by increased 6-minute walk time and quality of life index score (QOLs). **The remodeling of the LV takes at least 3 or more months.** On average, the LV systolic and diastolic dimensions decrease significantly following prolonged CRT. In studies in which biventricular (Bi-V) pacing was switched off after prolonged synchronized pacing, the systolic benefits disappeared rapidly; however, the LV dimensions were maintained for a longer period of time, suggesting that actual LV remodeling took place during CRT. There is also evidence that CRT may lead to electrical remodeling of the heart. In patients with LBBB or IVCD, CRT led to shortening of the duration of the native QRS complex. More recently, evidence from randomized clinical trials powered for mortality, in addition to symptomatic improvement, supports the use of CRT alone or in combination with an ICD in patients with ischemic and nonischemic etiologies of severe LVD.

VI. SUMMARY OF MAJOR CLINICAL TRIALS OF CRT. Most clinical trials evaluating CRT have addressed its role in patients in normal sinus rhythm (NSR) with severe LVD, class III to IV HF symptoms refractory to medical therapy, and indirect evidence of mechanical dyssynchrony represented by prolonged QRS duration (on average, > 120 milliseconds). More recently, large trials have focused on the benefits of CRT in patients with less symptomatic HF (NYHA classes I and II).

A. PATH-CHE. A longitudinal crossover study of 41 patients evaluating CRT (Bi-V or LV pacing) versus no therapy. Primary end points of peak Vo_2 , 6-minute walk, NYHA class, and QOLS significantly improved during CRT.

B. MUSTIC. A small prospective randomized trial powered for symptomatic improvement as measured by hospitalization, 6-minute walk, and QOLS in patients in NSR or with atrial fibrillation at the time of enrollment. The trial showed significant improvements with CRT, and the benefit was similar in NSR and atrial fibrillation.

C. MIRACLE. The MIRACLE trial, completed in late 2000, randomized 453 patients with advanced HF and a QRS duration ≥ 130 milliseconds to CRT versus conventional therapy for HF. The trial revealed significant improvements in peak Vo_2 , consumption, 6-minute hall walk, QOLSs, EF, NYHA class, and treadmill exercise times with CRT compared with controls. This trial led to the approval of CRT devices by the Food and Drug Administration.

D. MIRACLE-ICD. Very similar to MIRACLE, the MIRACLE-ICD trial was a moderate-sized prospective randomized trial evaluating the safety and efficacy of combining CRT with ICD therapy for a composite end point of mortality, hospitalization, and symptomatic improvement. At 6 months follow-up, the CRT-ICD arm had a significant improvement in the composite end point. Combining CRT with ICD was deemed safe.

E. CARE-HF. The CARE-HF was a large, open-label randomized controlled trial powered to assess mortality benefit with best medical therapy plus CRT versus medical therapy alone in patients with ischemic and nonischemic etiology of LVD. In addition to the conventional dyssynchrony criteria of QRS duration > 150 milliseconds, the trial was the first to implement echocardiographic markers of mechanical dyssynchrony in those patients with QRS duration between 120 and 150 milliseconds. At 3 years of

follow-up, the primary end point of all-cause mortality and hospitalization was significantly different in favor of the CRT group. Furthermore, the secondary end point of all-cause mortality reached statistical significance after 3 years of follow-up, and the survival curves continued to separate. The number needed to treat with CRT to save one life was estimated at nine patients.

- F. COMPANION.** A large, open-label randomized (1:2:2) prospective trial powered for mortality and hospitalization benefit in patients with ischemic and nonischemic etiologies of LVD comparing medical therapy versus CRT versus CRT-D. In addition to conventional QRS criteria for CRT, patients also had to have had one episode of hospitalization for HF in the year prior to randomization. The primary end point of all-cause mortality and hospitalization was significantly different in the device groups as compared with the medically treated group. The secondary end point of all-cause mortality was significantly different in the CRT-D group as compared with the medical controls. The CRT group showed a strong trend toward mortality benefit that did not reach statistical significance. The trial was not powered to compare mortality benefits between the two device groups. In the CRT-D group, the mortality benefit was noticed shortly after the beginning of the trial, as compared with 6 to 12 months after study initiation in CARE-HF. The early mortality benefit in this trial was thought to be ICD related. The later benefits were attributed to both ICD and CRT therapies. The results of this trial led to approval of combined CRT-D therapy in the above population of patients.

VII. MAJOR TRIALS OF CRT IN MINIMALLY SYMPTOMATIC HF

- A. REVERSE.** The REVERSE study, published in 2008, was a large randomized, double-blind trial designed to assess whether CRT in addition to medical therapy could delay progressive myocardial remodeling and/or prevent HF progression. The study enrolled 610 patients with a 2:1 enrollment design such that 419 patients received a CRT-D device and 191 patients received an ICD alone. Inclusion criteria for the study were NYHA class I or II symptoms, a left ventricular ejection fraction (LVEF) $\leq 40\%$, a left ventricular end-diastolic dimension ≥ 55 mm, NSR, and a QRS duration ≥ 120 milliseconds. The primary end point of REVERSE was a novel clinical composite end point developed by Packer and colleagues, which rates patients as “improved,” “unchanged,” or “worsened” based on the combination of mortality status, hospitalizations due to HF, withdrawal of consent, and worsening NYHA class. The American arm of the study concluded at 12 months, with the European arm proceeding to 24 months. While there was no difference in the primary end point at 12 months, patients in the CRT arm derived significantly greater reductions in the left-ventricular end-systolic volume index and the left-ventricular end-diastolic volume index, respectively, and improvement in LVEF compared with those without CRT. During the 12-month follow-up period, there was no difference in mortality between the two groups; however, CRT significantly lowered HF hospitalizations. In the European arm of the trial in which follow-up was continued for an additional year, the benefit of CRT in inducing reductions in LV volumes and improvement in LVEF persisted at 24 months.

- B. MADIT-CRT.** MADIT-CRT, published in 2009, sought to determine the impact of CRT on HF hospitalizations and all-cause mortality in patients with NYHA class I or II HF symptoms. This multicenter, unblinded study randomized 1,820 patients in North America and Europe with an LVEF $\leq 30\%$, NYHA class I or II symptoms (patients with nonischemic cardiomyopathy and NYHA class I symptoms were excluded), NSR, and a QRS duration ≥ 130 milliseconds to a CRT-D device or an ICD alone. The primary end point for the study was death from any cause or a nonfatal HF event. At a mean follow-up of 2.4 years, patients in the CRT arm had a significantly lower incidence of the primary end point compared with the ICD alone arm. Similar to what was shown in REVERSE, patients in the CRT arm of

MADIT-CRT realized significantly greater improvements in myocardial structure and function compared with those without CRT.

C. RAFT. The RAFT trial which began enrollment in 2003 was a large, double-blinded, randomized controlled trial of 1,798 patients with NYHA class II or III symptoms, an LVEF $\leq 30\%$, and a QRS duration ≥ 120 milliseconds (or a paced QRS > 200 milliseconds), which compared therapy with CRT-D versus that with an ICD alone. Originally, the trial sought to determine whether CRT in addition to an ICD would improve survival in patients with class II and III symptoms. After publication of the CARE-HF trial and subsequent guideline changes, however, the protocol was altered in early 2006 to include only patients with NYHA class II symptoms. Of 894 patients receiving a CRT-D device in the RAFT trial, 79.2% had NYHA class II symptoms. For inclusion, patients had to either be in NSR or have rate-controlled permanent atrial fibrillation or flutter. The primary end point of all-cause death or HF hospitalization occurred in 33.2% of the CRT-D group and in 40.3% of the ICD only group over a follow-up of 40 ± 20 months. In looking at only patients with NYHA class II symptoms, patients in the CRT arm had reductions in the primary end point as well as in both cardiovascular and all-cause mortality and hospitalizations due to HF.

VIII. NONRESPONDERS. Up to 30% of patients who receive CRT based on current QRS criteria fail to benefit from the therapy depending on one's definition of response. Their symptoms do not improve or worsen, and there is no echocardiographic evidence of reverse ventricular remodeling. A clear etiology of the lack of improvement from CRT in those patients has not yet been elucidated. One of the possibilities is that QRS duration alone is not a good indicator of mechanical dyssynchrony, and some patients, despite prolonged QRS duration, do not have mechanical dyssynchrony and worsen when Bi-V pacing is commenced. In subjects with normal baseline LV contraction, Bi-V or LV free wall pacing has an inferior hemodynamic profile when compared with native conduction. Therefore, it becomes important that CRT be only offered to those that truly have asynchronous contraction.

Another potential explanation for the lack of CRT benefit in certain patients is the presence of myocardial scar in the LV free wall territory. Areas of fibrous myocardium are electrically and mechanically nonviable; therefore, pacing at those sites may be of little value.

Lead position may play an important role in nonresponse. Typically, in nonischemic dilated cardiomyopathy with LBBB, the posterobasal segment has the most delayed activation and contraction. This is not always the case in patients with ischemic etiology of LVD, where occasionally the inferior wall becomes activated the latest. It is conceivable that, due to limitations in the myocardial venous system, inadvertent placement of the LV lead in an area that is not significantly delayed may lead to adverse hemodynamic effects. Trials are underway using echocardiographic techniques to determine the latest activated segment with implanters targeting placement of the LV lead in or near this segment.

IX. CURRENT GUIDELINES AND RECOMMENDATIONS. Based on the inclusion criteria from the available large randomized trials at that time (see Table 56.2), the AHA/ACC 2008 Guideline Update for the Diagnosis and Management of Chronic Heart Failure in the Adult gives CRT a class I indication (level of evidence A) in patients with ischemic or nonischemic etiology of depressed LV function, EF $\leq 35\%$, severe HF symptoms, and NYHA class III or IV, on optimal medical therapy, in sinus rhythm with wide QRS complex ≥ 120 milliseconds, and with LV end-diastolic diameter ≥ 55 to 60 mm. The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology, in collaboration with the European Heart Rhythm Association, provides the following recommendations for CRT.

TABLE 56.2 Current Recommendations for the Use of Cardiac Resynchronization Therapy in Patients with Heart Failure

Recommendation	Class	Level of evidence
Symptomatic HF (NYHA class III or ambulatory class IV) despite optimal medical therapy, with an LVEF $\leq 35\%$, normal sinus rhythm, and a wide QRS complex (≥ 120 milliseconds), should be treated with CRT/D	I	B
Symptomatic HF (NYHA class III or ambulatory class IV) despite optimal medical therapy, with an LVEF $\leq 35\%$, and a frequent dependence on ventricular pacing should be treated with CRT/D	IIa	C
Symptomatic HF (NYHA classes III or ambulatory class IV) despite optimal medical therapy, with an LVEF $\leq 35\%$ and atrial fibrillation, should be treated with CRT/D	IIa	B
Symptomatic HF (NYHA class I or II) despite optimal medical therapy, with an LVEF $\leq 35\%$, who are undergoing implantation of a permanent pacemaker or ICD with anticipated ventricular pacing should be treated with CRT	IIb	C
Asymptomatic patients with reduced EF in the absence of other indications for pacing should not be treated with CRT/D	III	B
CRT is not indicated in patients whose functional status and life expectancy are limited by predominantly noncardiac conditions	III	C

CRT, cardiac resynchronization therapy; CRT/D, CRT with a defibrillator; EF, ejection fraction; HF, heart failure; ICD, implantable cardioverter–defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association.

Adapted from the ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm.

- A. The use of CRT or CRT-D is recommended in patients with HF who remain symptomatic in NYHA classes III–IV despite optimal medical therapy and with an LVEF $\leq 35\%$, LV dilation with LV end-diastolic diameter > 55 mm, NSR, and wide QRS complex (≥ 120 milliseconds) (class I, level of evidence A for CRT; class I, level of evidence B for CRT-D).
- B. The use of CRT is also recommended in patients with HF with NYHA classes III–IV despite optimal medical therapy and with an LVEF $\leq 35\%$, LV dilation, and a concomitant indication for permanent pacing (first implant or upgrade of conventional pacemaker) (class IIa, level of evidence C).
- C. The use of CRT is also recommended in patients with HF who remain symptomatic in classes III–IV despite optimal medical therapy and with an LVEF $\leq 35\%$, LV dilation, permanent atrial fibrillation, and indication for AV junction ablation (class IIa, level of evidence C).
- D. The use of CRT is also recommended in patients with HF who remain symptomatic in classes III–IV despite optimal medical therapy and with an LVEF $\leq 35\%$, QRS ≥ 130 milliseconds, permanent atrial fibrillation, and indication for AV junction ablation (class IIa, level of evidence C).

X. IMPLANTATION PROCEDURE. Unlike conventional transvenous pacemaker or ICD implantation that requires lead placement in the right atrium and/or the right ventricle only, Bi-V pacing requires LV lead implantation. Initially, this was achieved via a

thoracotomy; however, currently up to 98% of Bi-V devices are placed via a transvenous approach. Although now used infrequently, some patients are still referred for a thoracotomy after a failed transvenous approach. Because most patients who qualify for CRT are also candidates for an ICD, current CRT devices have a combined pacemaker/ICD capability. The hybridization of CRT and ICD therapy increases the complexity of programming, follow-up, and troubleshooting of such devices.

The procedure is performed in an electrophysiology laboratory under sterile conditions. All patients receive preprocedural antibiotics at least 30 minutes before the procedure. A subcutaneous pocket is first prepared, making sure that appropriate hemostasis is achieved. Bi-V device implantation, due to the increased risk imposed by possible coronary sinus (CS) perforation, requires complete reversal of anticoagulation. Typically, a cephalic or axillary vein approach to venous access is used. The right atrial and RV leads are implanted in a fashion similar to a pacemaker or ICD implantation. The LV lead is placed through the CS into a CS branch on the lateral free wall of the left ventricle. Performing an occlusive CS venogram may help identify the appropriate vein. Various sheaths, catheters, and guidewires are available to cannulate the CS and advance the pacing lead into the appropriate vein. While the optimal site for LV lead placement is controversial, many experts agree that anterior and apical positions are suboptimal. Once the lead is advanced, its location should be confirmed by fluoroscopy, typically in the left anterior oblique (LAO) view. The goal is to document base to mid-posterolateral LV lead placement and maximal LV–RV lead separation in the LAO view. A steep angulation in the LAO view tends to be most accurate. It has been shown that LV–RV interlead distance on the **lateral chest radiograph** is predictive of CRT response. Pacing thresholds are acceptable if < 3 V at 0.5 milliseconds. Diaphragmatic capture is excluded by high-voltage pacing. If high pacing threshold or diaphragm capture occurs, the lead should be repositioned. CS trauma is frequent during lead placement, and it may range from dissection to frank perforation. Because the pressure in the venous system is low, serious sequelae are unusual and cardiac tamponade rarely results. After adequate LV lead placement and confirmed appropriate LV lead function, care must be taken during guidewire, CS platform, and stylet removal, so as not to disrupt lead position. Lead dislodgement occurs in as many as 5% to 10% of implantations. The time frame for the majority of dislodgements is the first 24 to 48 hours postimplantation, when patients resume activity. For that same reason, patients are encouraged to ambulate while still in-house to prevent any out-of-hospital dislodgement, which may have more serious consequences.

XI. PROGRAMMING AND FOLLOW-UP. Currently, multiple configurations for Bi-V pacing exist. The available pacing configurations vary by device manufacturer. Changing configurations for pacing can be very useful in cases of poor thresholds or diaphragmatic stimulation.

Ventricular pacing must be **continuous** during CRT in order to obtain maximal benefit. Typically, DDD mode with a short AV delay (80 to 110 milliseconds) to prevent native conduction is employed. If atrial pacing is undesirable due to increased incidence of atrial fibrillation or altered left-sided AV timing, VDD mode may be used. Ventricular pacing is usually simultaneous or with a slight V-V delay. Given the two ventricular inputs (right ventricle and left ventricle), one could foresee that ventricular timing cycles could be quite complex during Bi-V pacing. Therefore, in most devices, the right ventricle is the only sensing chamber.

Follow-up of CRT devices includes a 12-lead ECG to assess for Bi-V capture and device interrogation to assess pacing thresholds. In those patients who are deemed non-responders, echocardiography may be used to optimally time the AV delay based on Doppler mitral valve inflow patterns or Doppler aortic velocity time integral. Generally speaking, interventricular timing (V-V interval), although programmable, is not taken into consideration during CRT programming. Limited studies suggest that AV

programming may lead to a better acute hemodynamic response to CRT in certain patients. The value of VV optimization is of considerable debate. In addition, specialized nonresponder clinics may help troubleshoot device issues, treat arrhythmias, maximize CHF medications, and optimize the AV interval. While such clinics are limited mostly to specialized centers, such clinics have been shown to convert some nonresponders to responders.

XII. LOSS OF CRT. CRT is transiently interrupted in up to 35% of patients and permanently interrupted in 5% at 2 years of follow-up. Fortunately, restoration of CRT can be accomplished via nonsurgical means in the majority of the cases. Pacing parameters, occurrence of atrial arrhythmias, and lead malfunction or dislodgement are common causes of CRT interruption. The goal of continuous pacing during CRT should be reflected in appropriate programming algorithms. Typically, the AV conduction status is what influences continuous delivery of Bi-V pacing. Because the majority of patients who require CRT have an intact AV node, any parameters that allow for preferential native conduction will reduce CRT delivery. Keeping the AV interval as short as possible while maintaining proper ventricular loading is therefore optimal. Atrial arrhythmias are common in advanced HF. Rapid ventricular rate during atrial arrhythmias with rapid AV conduction inactivates Bi-V pacing due to the upper tracking rate limit. Keeping patients in NSR is therefore desirable. Any evidence of lead malfunction or displacement should be dealt with promptly by reintervention. The loss of CRT results in symptomatic deterioration in HF and hospital admission in many instances.

XIII. FUTURE DIRECTIONS. While CRT has emerged as one of the most important advances in the treatment of LVD over the last 15 years, several important questions remain. Despite the myriad of parameters of mechanical dyssynchrony that are available, none has been shown to be a practical and reliable predictor of response. Developing a measure of dyssynchrony that predicts response accurately and can be used across multiple care settings remains a challenge. Whether CRT has a role in patients with a narrow QRS duration remains in question. While the ReTHINQ trial failed to show benefit in this population, a two-dimensional measure of dyssynchrony was used. In the ongoing ECHO-CRT trial, a three-dimensional dyssynchrony measure will be employed, which should shed considerable light on the applicability of CRT in this population. Lastly, the role of CRT in patients without a native or RV-paced LBBB morphology is an area of considerable controversy. Patients with right bundle branch block (RBBB) have early activation of the left ventricle and late activation of the right ventricle, calling into question the role of LV pacing for these patients. Still, most patients with RBBB have a wider QRS duration than would be expected from having a “pure” RBBB alone. This implies additional left-sided delay that may be mitigated by CRT. While retrospective studies have certainly called into question the benefits of CRT in this population, currently, there is no prospective randomized trial to provide a more definitive answer. Patients with nonspecific IVCD are a heterogeneous population, likely with both right- and left-sided delay. In retrospective studies, the response rate of this population is more akin to those with RBBB than LBBB; however, the studies have been small.

XIV. SUMMARY. CRT has emerged as an effective therapy in patients with LVD refractory to CHF medications and a wide QRS duration. Major clinical trials have proven significant morbidity and mortality benefits from CRT first in patients with advanced heart and more recently in those with minimal symptoms. The issue of nonresponse to CRT continues to be a major problem and much ongoing research continues to be dedicated to predicting which patients will respond to this therapy. While many studies have shown some predictive ability of various imaging modalities, none to date has been shown to be a reliable predictor of response that could be utilized across multiple

centers. While the response to CRT in patients with a native LBBB or RV-paced rhythm is well documented, the response in patients with RBBB or a nonspecific IVCD continues to be debated.

ACKNOWLEDGMENTS: *The author wishes to acknowledge the contribution of Dr. Peter Borek to the previous edition of this chapter.*

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SECTION

XI

Common Cardiology Procedures

EDITORS

Brian P. Griffin

Thomas D. Callahan

Venu Menon

Common ECG Patterns

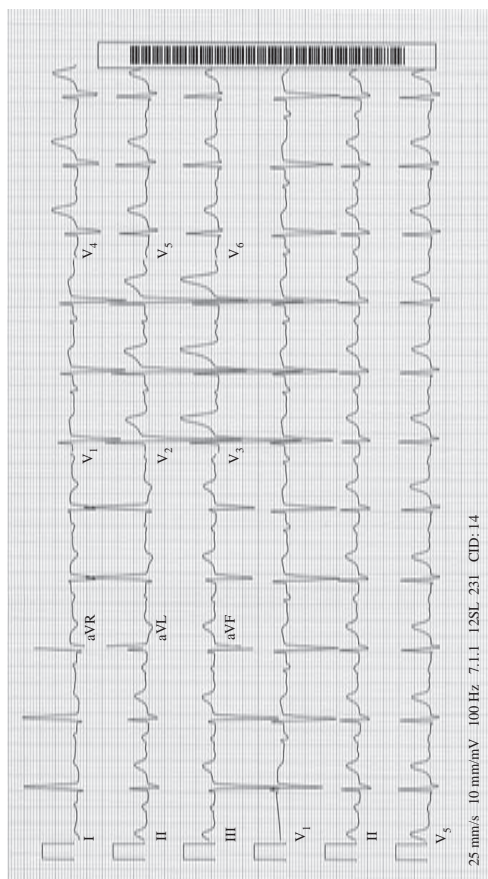


FIGURE 57.1 Left ventricular hypertrophy (LVH).

- Note that the R wave in lead aVL is > 11 mm, and the R wave in lead V_5 or $V_6 + S$ wave in lead V_1 is > 35 mm.
- Left axis deviation is present.
- Left atrial enlargement, which often occurs with LVH, is also present (the terminal negative portion of the P wave in lead V_1 is ≥ 1 mm in depth and ≥ 40 ms in duration, and the P wave is broad in inferior leads).

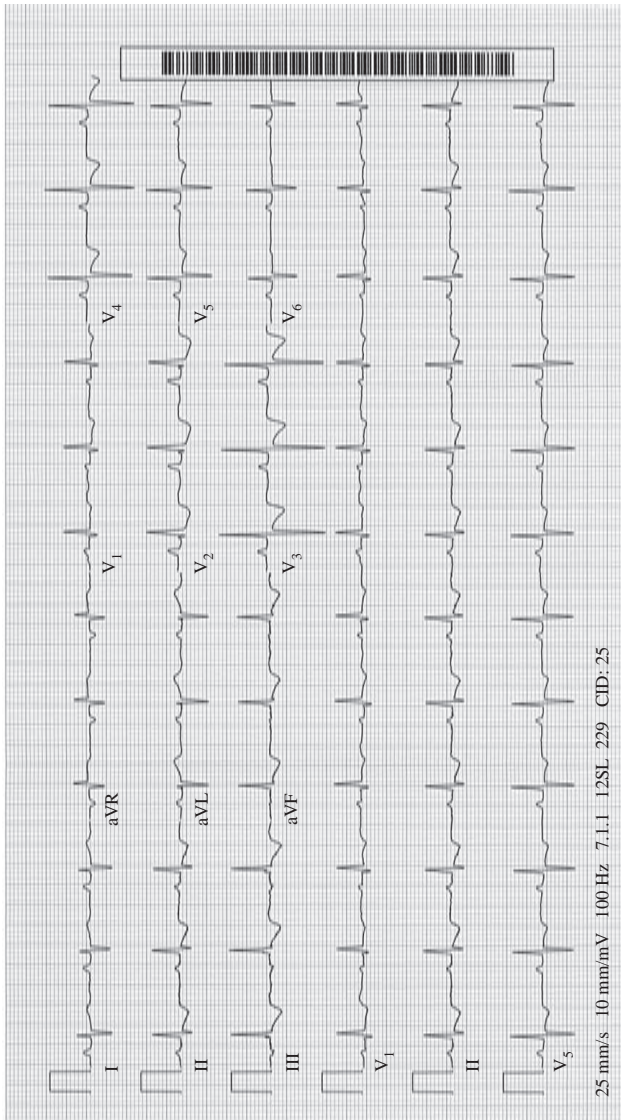


FIGURE 572 Right ventricular hypertrophy.

- The R wave in lead V_1 is > 6 mm, and there is right axis deviation (QRS axis $> 100^\circ$).
- Other criteria include an R/S ratio in lead $V_1 > 1$ and an R/S ratio in lead V_5 or $V_6 \leq 1$.

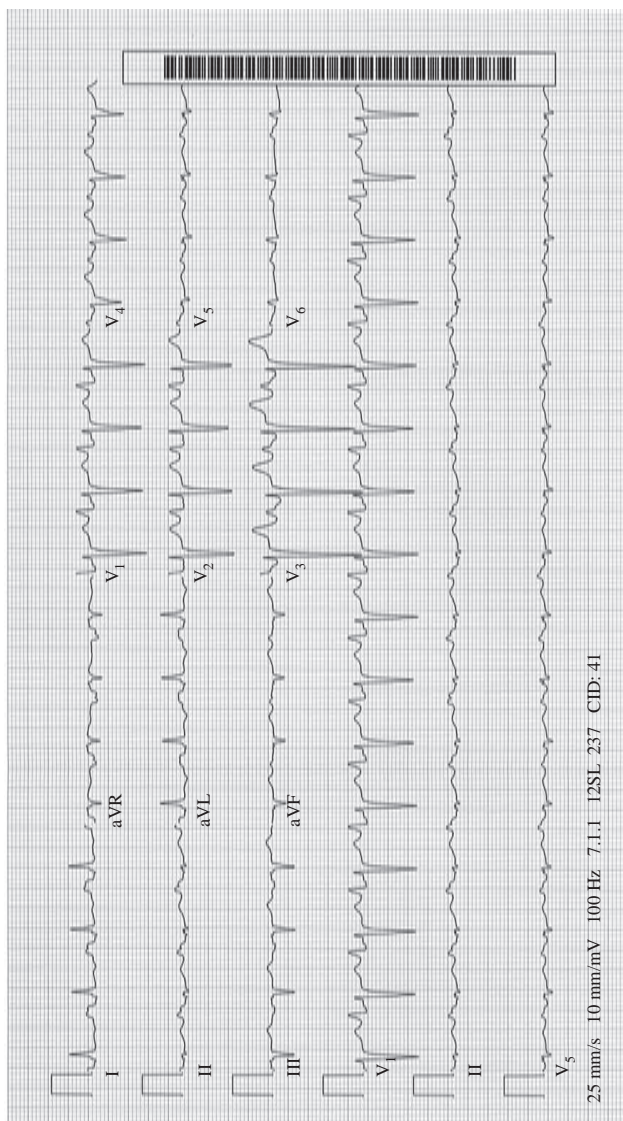


FIGURE 57.3 Batrial enlargement.

- Left atrial enlargement is indicated by the negative terminal portion of the P wave in lead V_1 and the broad P wave in inferior leads.
- Right atrial enlargement is indicated by the height of the P wave in inferior leads and lead V_1 .

Common arrhythmias

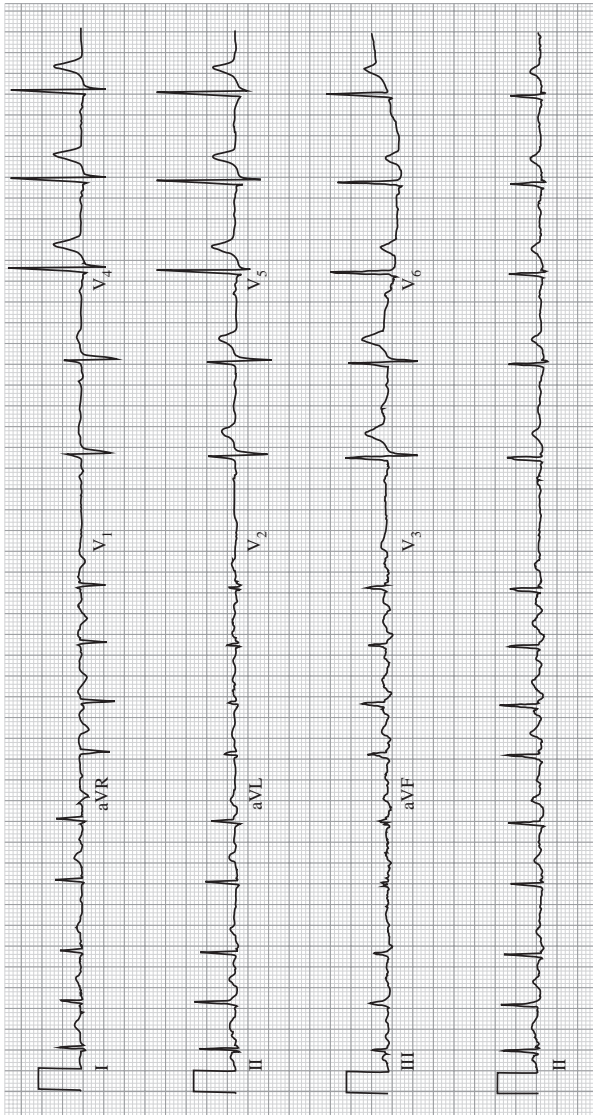


FIGURE 57.4 Atrial fibrillation.

- Irregular activity of the atria causes random oscillation of the baseline, and P waves are absent. The ventricular rate is irregularly irregular.
- The patient spontaneously converted to sinus rhythm midway through the rhythm strip.

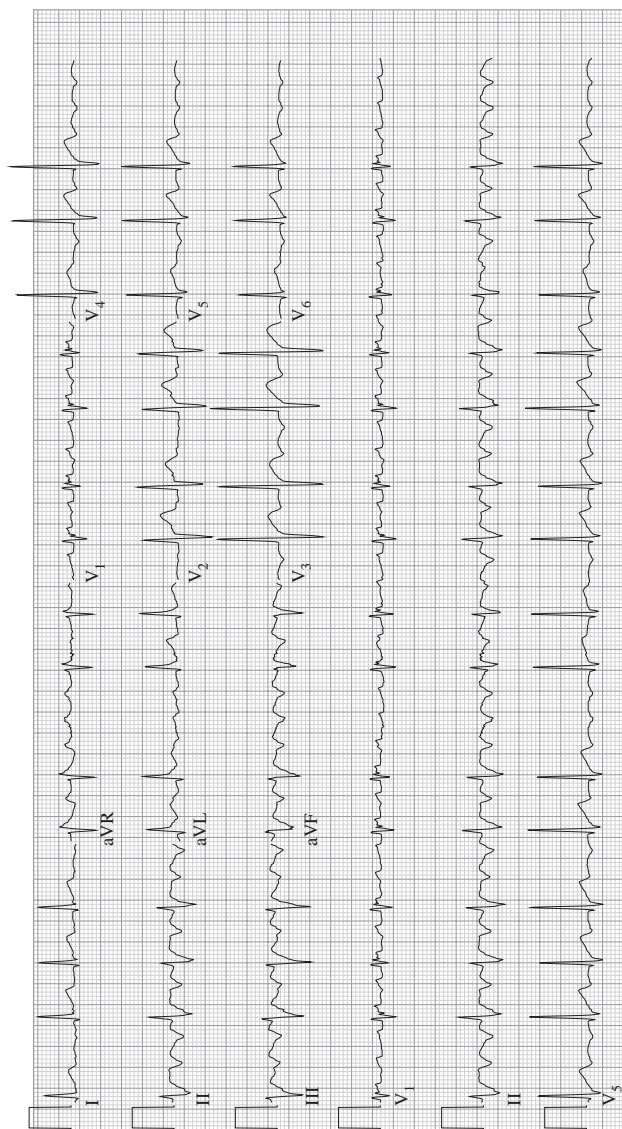


FIGURE 57.5 Typical atrial flutter.

- Flutter waves with a “sawtooth” appearance are present at around 300 beats/min. The waves are negative in inferior leads and positive in lead V_1 .

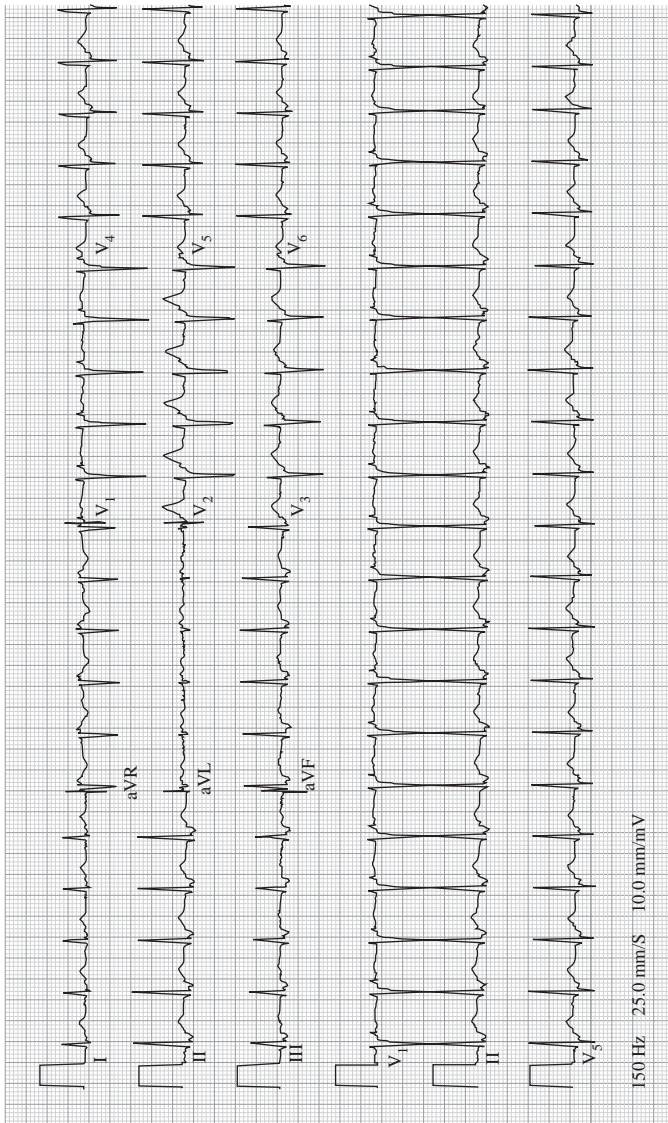


FIGURE 57.6 Atrioventricular (AV) nodal reentrant tachycardia.

- A regular, narrow QRS complex is present.
- A retrograde P wave is seen following the QRS complex in lead V₁ ("pseudo-R").

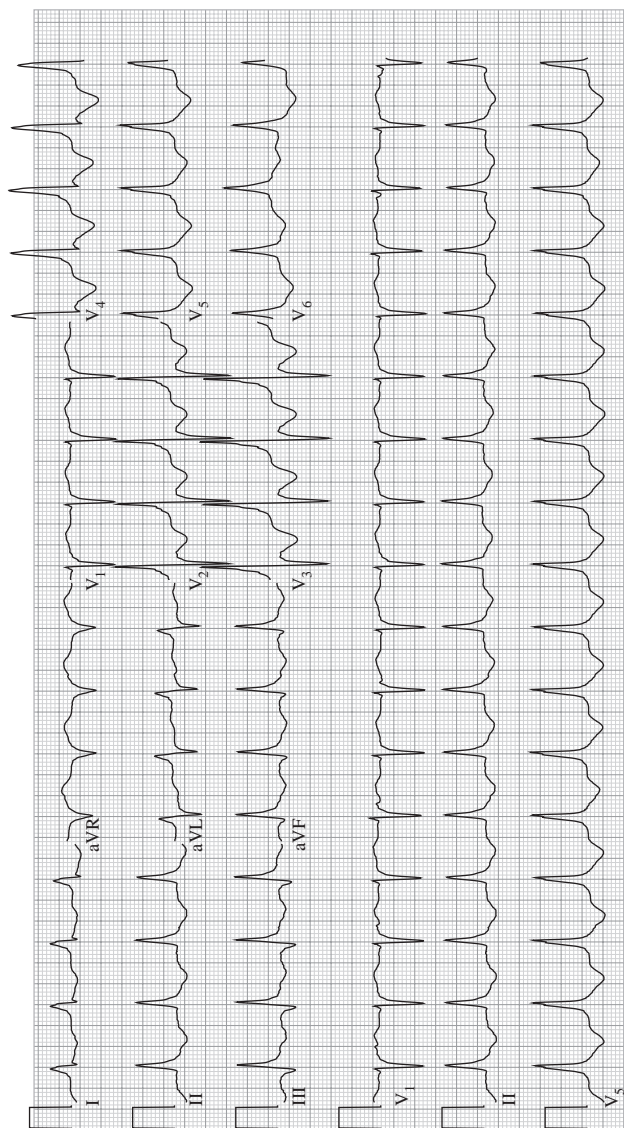


FIGURE 57.7 Ventricular tachycardia.

- A rapid, wide QRS complex is present. P waves are best seen in leads V_1 and II and are clearly dissociated from ventricular activity.

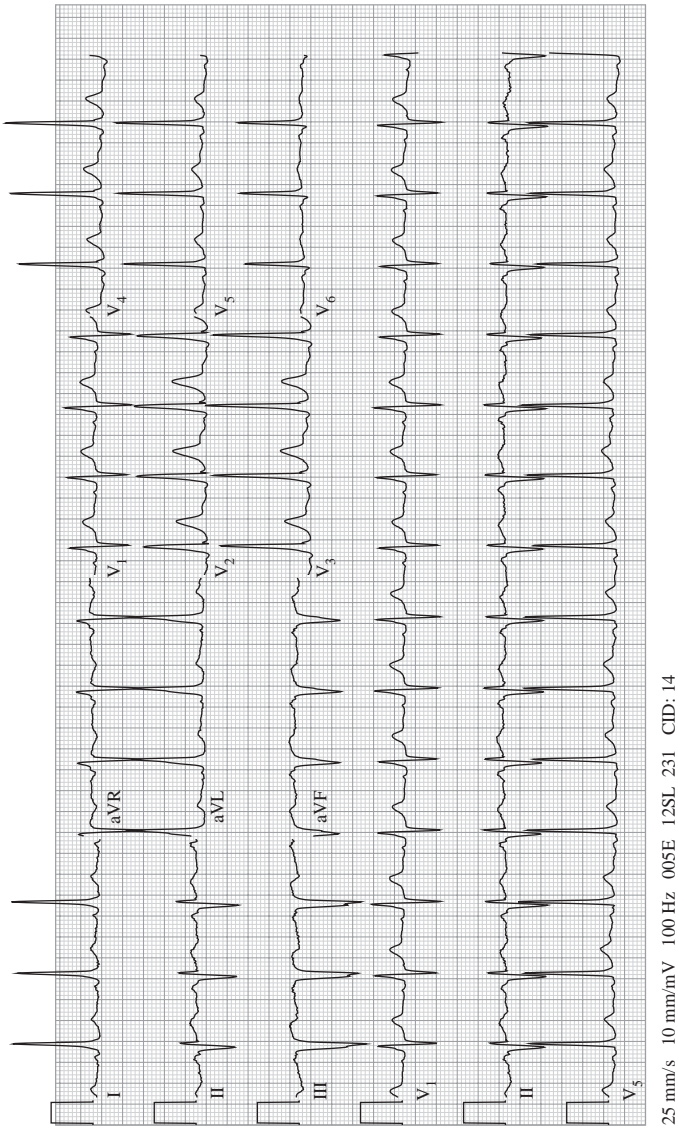


FIGURE 57.8 Wolff-Parkinson-White (WPW) pattern.

- Preexcitation of the ventricle causes a short PR interval and slurring of the initial portion of the QRS complex (delta wave).

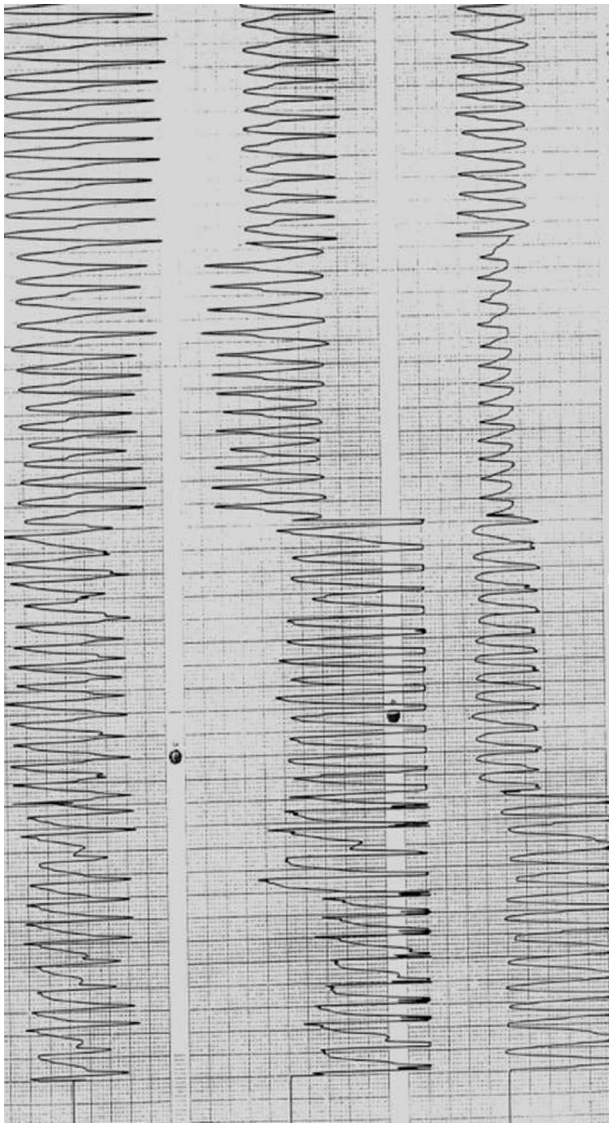


FIGURE 57.9 Atrial fibrillation with WPW.

- If atrial fibrillation develops, conduction to the ventricles can be very rapid. There is a varying degree of fusion between conduction through the AV node and conduction through the bypass tract, causing each beat to have a different morphology.

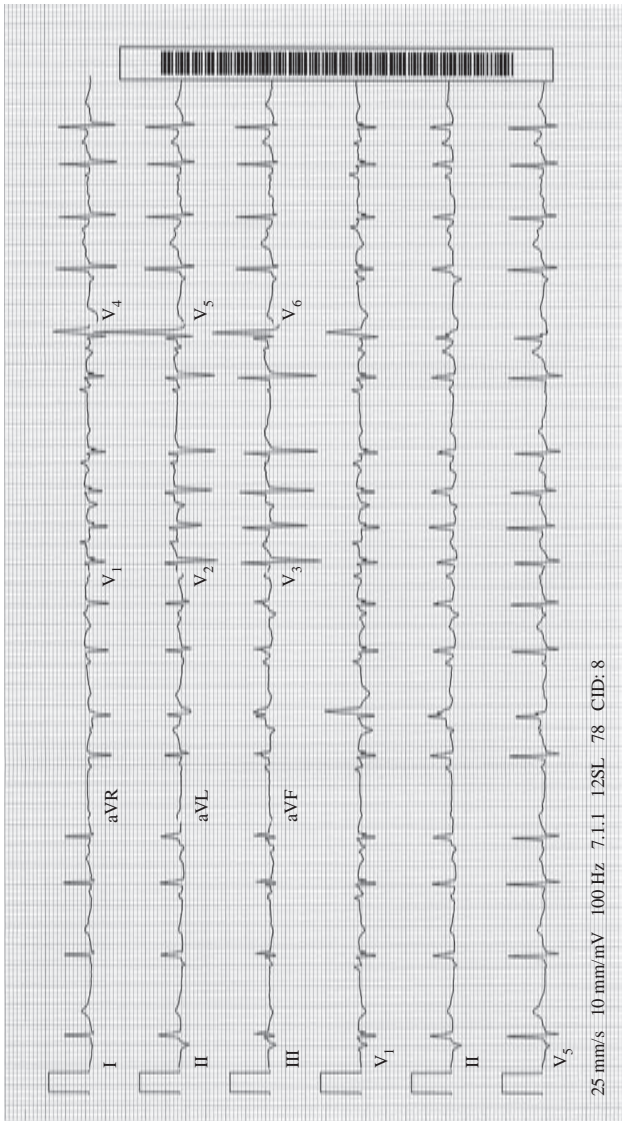
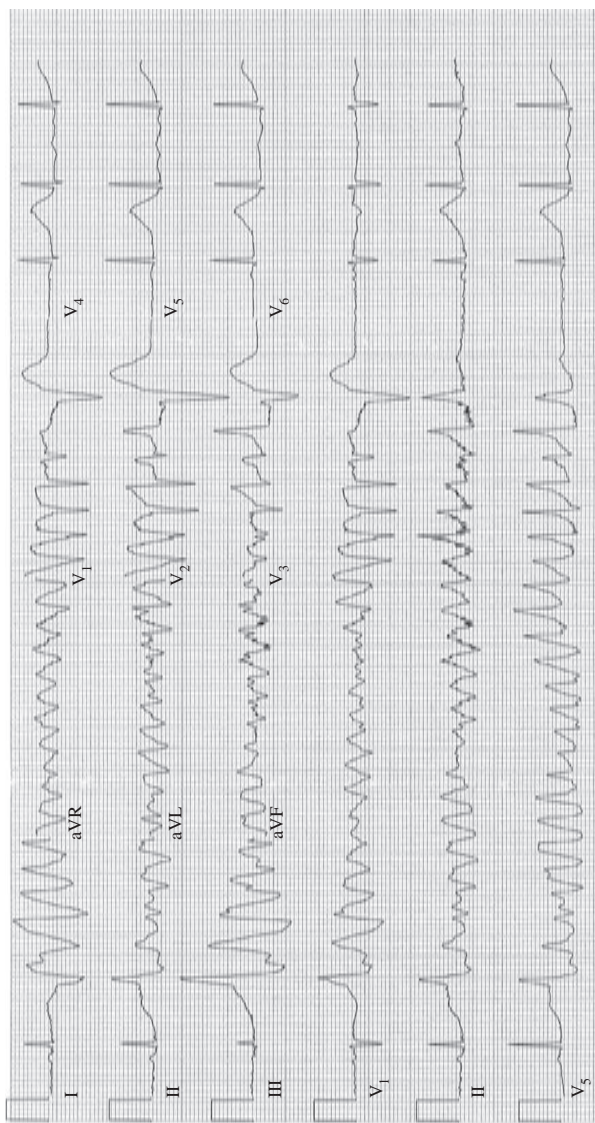


FIGURE 57.10 Multifocal atrial tachycardia.

- The atrial rate is rapid, and multiple P-wave morphologies are present.



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FIGURE 57.11 Torsades.

- A rapid ventricular rhythm with QRS complexes of varying axis (“twisting of the points”) is present.

Conduction disease

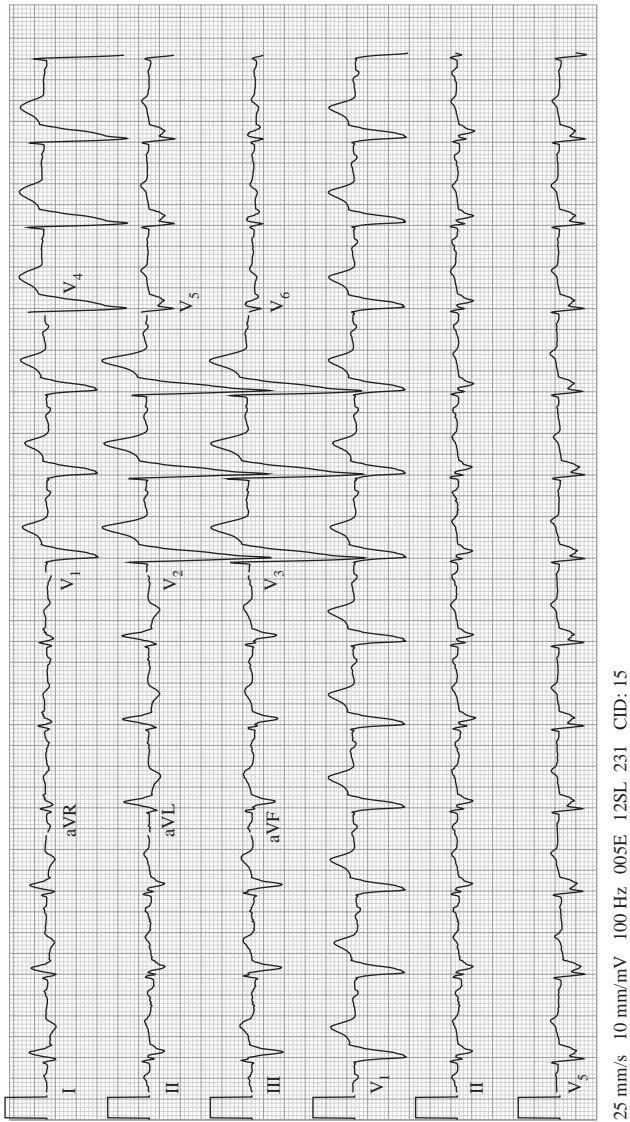


FIGURE 57.12 Left bundle branch block.

- The QRS duration is prolonged (> 120 ms).
- There is a broad R wave in leads I and V_6 , representing delayed activation of the left ventricle.
- The right precordial leads have an rS complex.
- There are ST-segment changes in the direction opposite to the major QRS deflection.

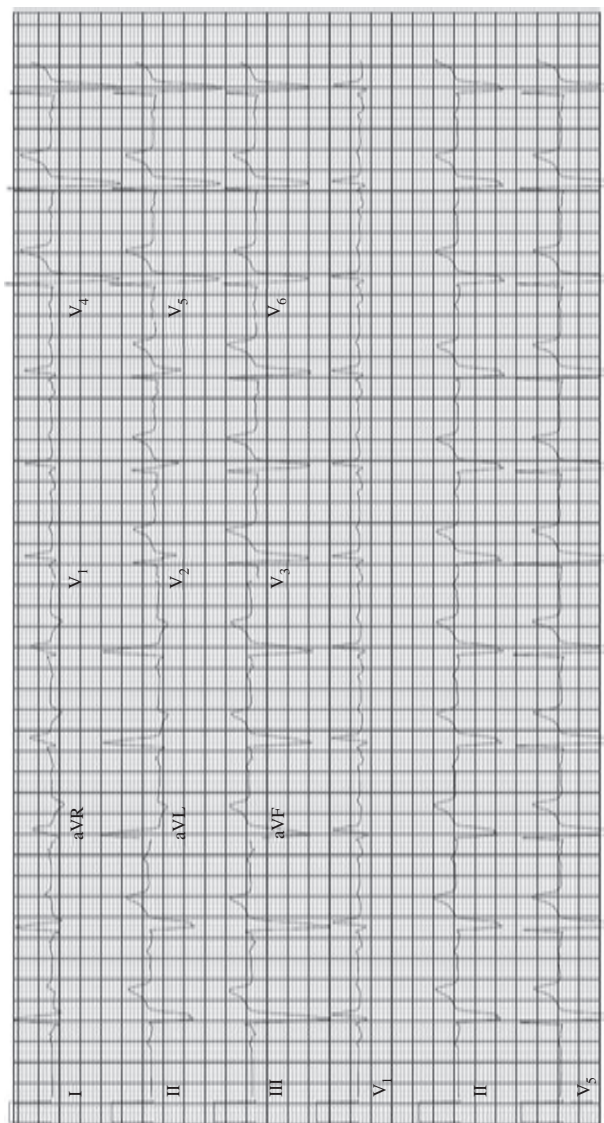


FIGURE 57.13 Right bundle branch block (RBBB) and left anterior fascicular block (LAFB).

- The QRS duration is prolonged beyond 120 ms.
- There is an rsR' pattern in leads V₁ and V₂, representing delayed activation of the right ventricle.
- Leads I, V₅, and V₆ have a wide, slurred S wave.
- LAFB is indicated by the presence of left axis deviation without another cause (inferior infarction, LVH, chronic obstructive pulmonary disease, and ostium primum atrial septal defect) and the rS complex in inferior leads.

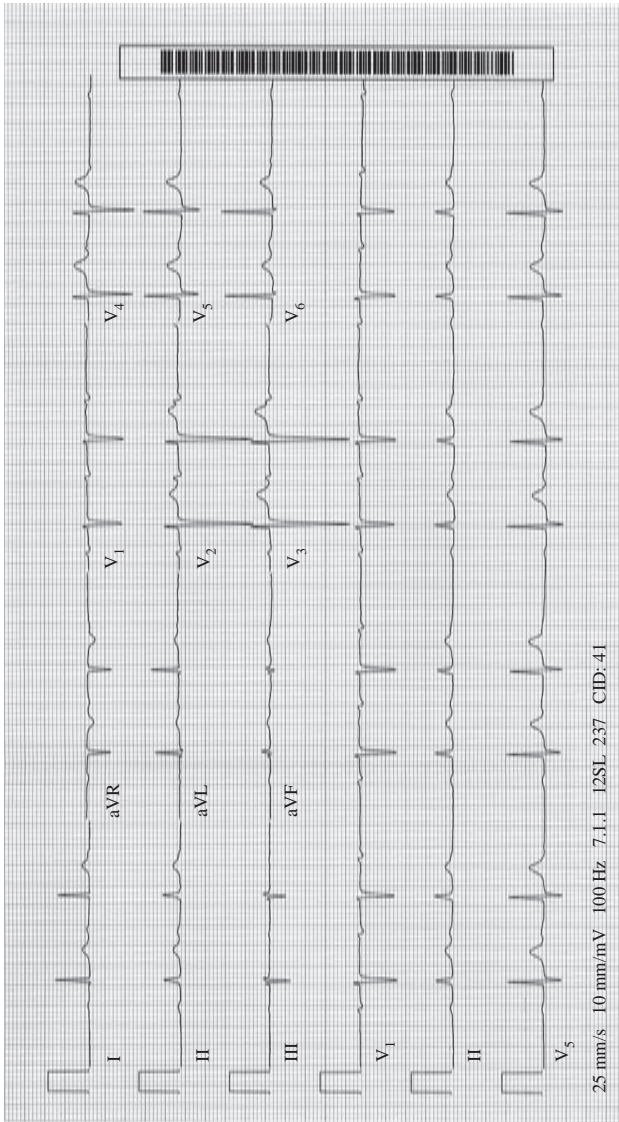


FIGURE 57.14 Second-degree Mobitz type I AV block.

- There is progressive prolongation of the PR interval until a P wave blocks.

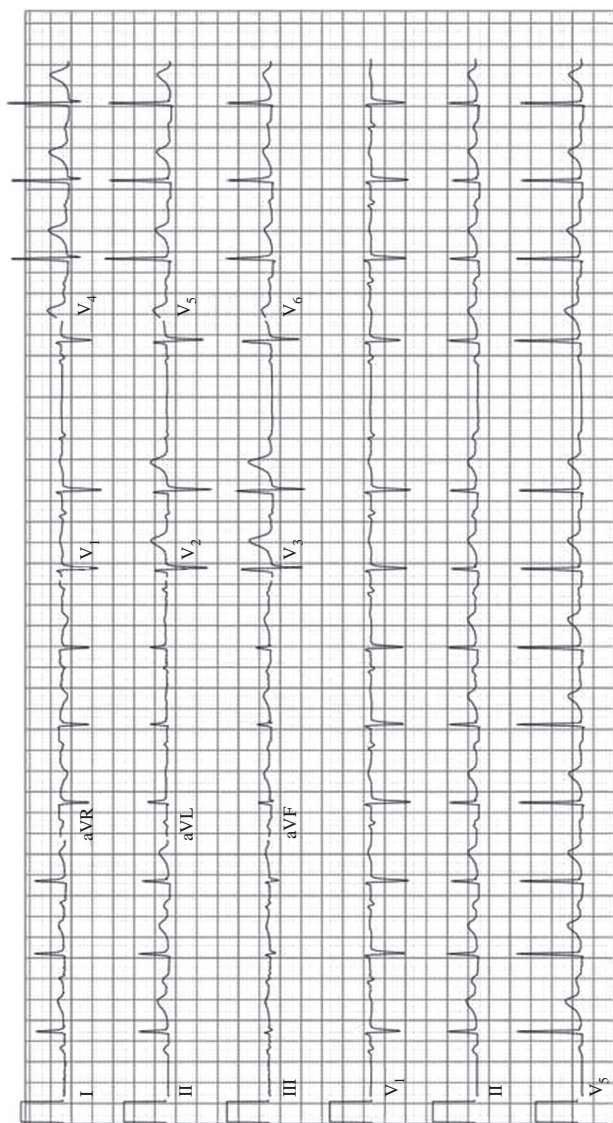


FIGURE 57.15 First-degree AV block and Mobitz type II second-degree AV block.

- The PR interval is more than 200 ms, indicating first-degree AV block.
- A P wave intermittently blocks. There is no lengthening of the PR interval prior to the dropped beat.

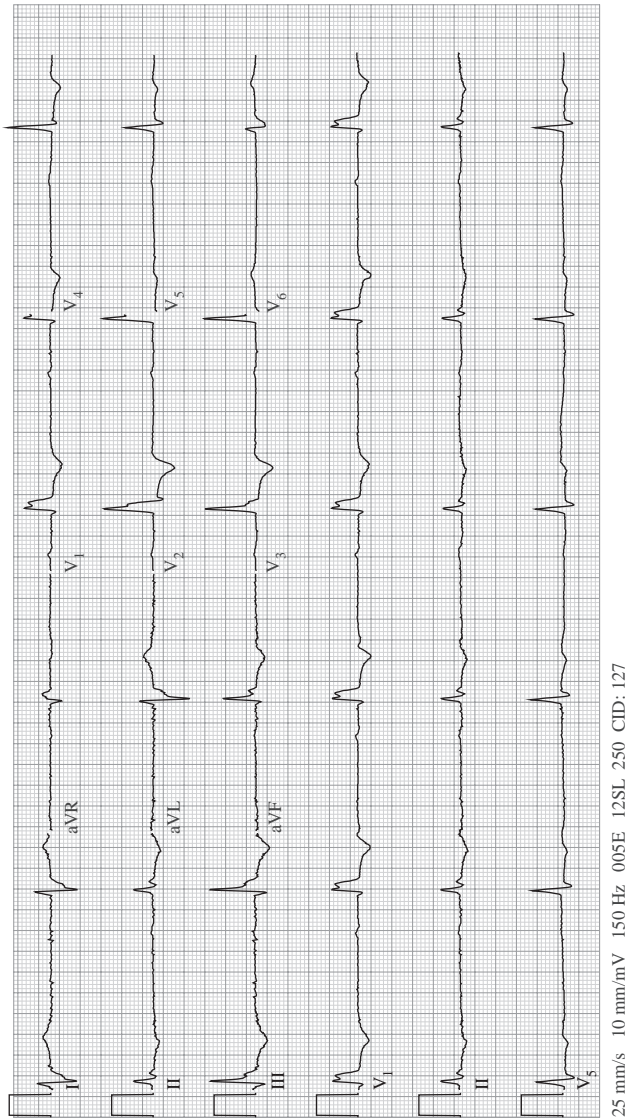
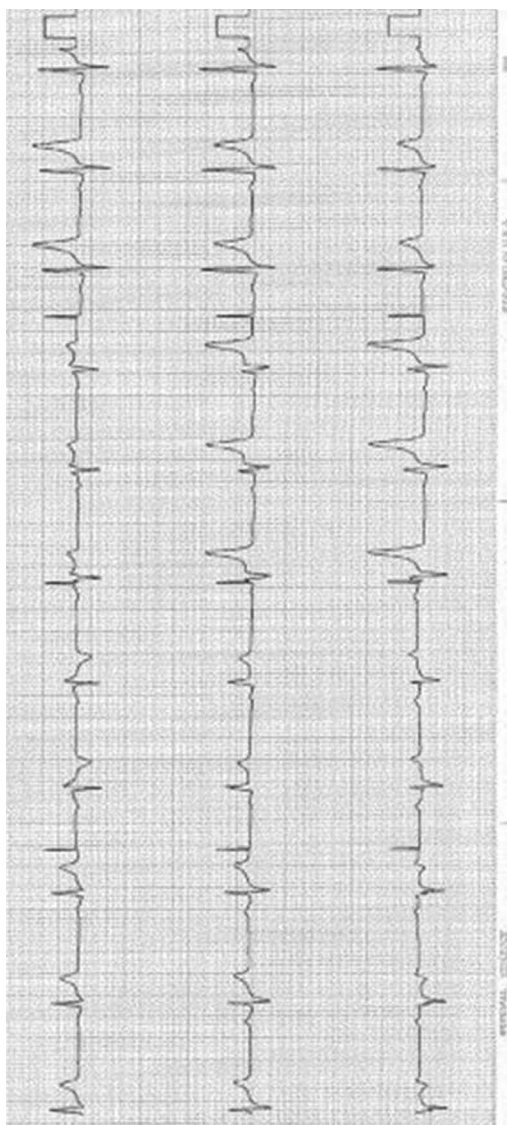


FIGURE 57.16 Complete heart block.

- P waves are not conducted to the ventricles, leading to atrial and ventricular rhythms that are independent of each other.
- The P-P and R-R intervals are constant, but the PR interval varies.

Metabolic disturbances

**FIGURE 57.17** Hyperkalemia.

- Tall, peaked T waves are present.
- The QT interval is short.

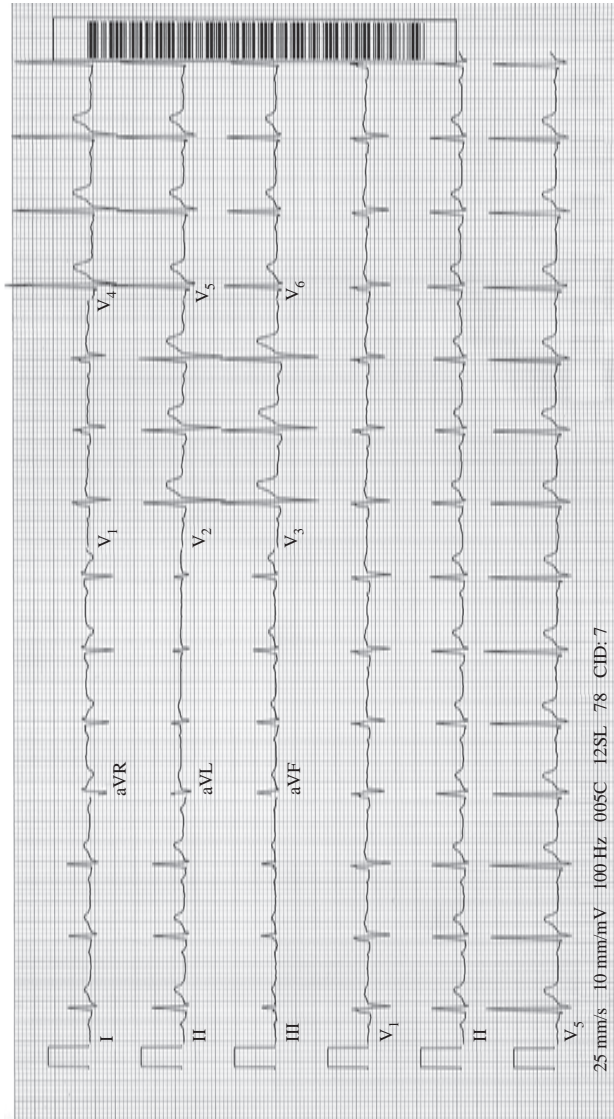


FIGURE 57.18 Hypercalcemia. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:552.

- The QT interval is short.

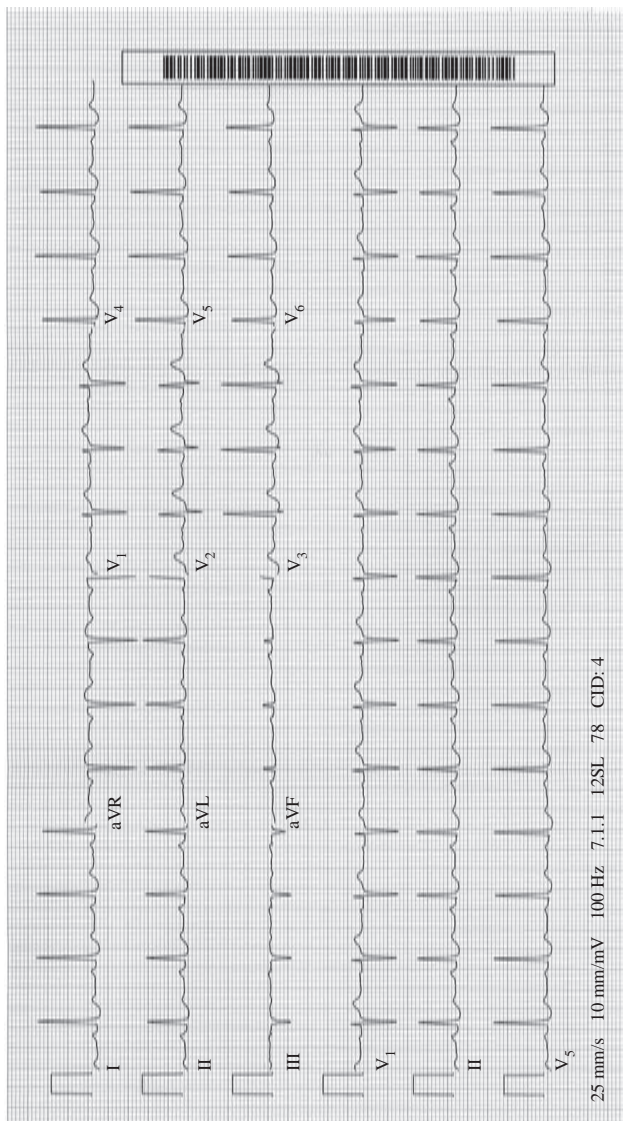


FIGURE 57.19 Digitalis effect.

- The ST segments sag downward and have upward concavity.
- The PR lengthens and the QT is short.

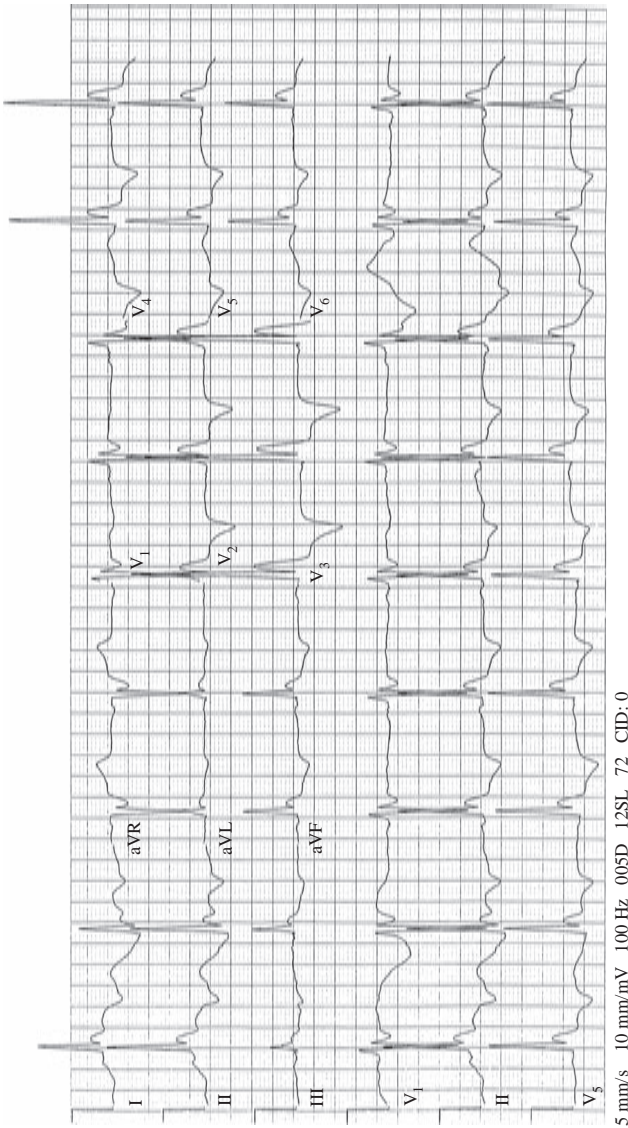
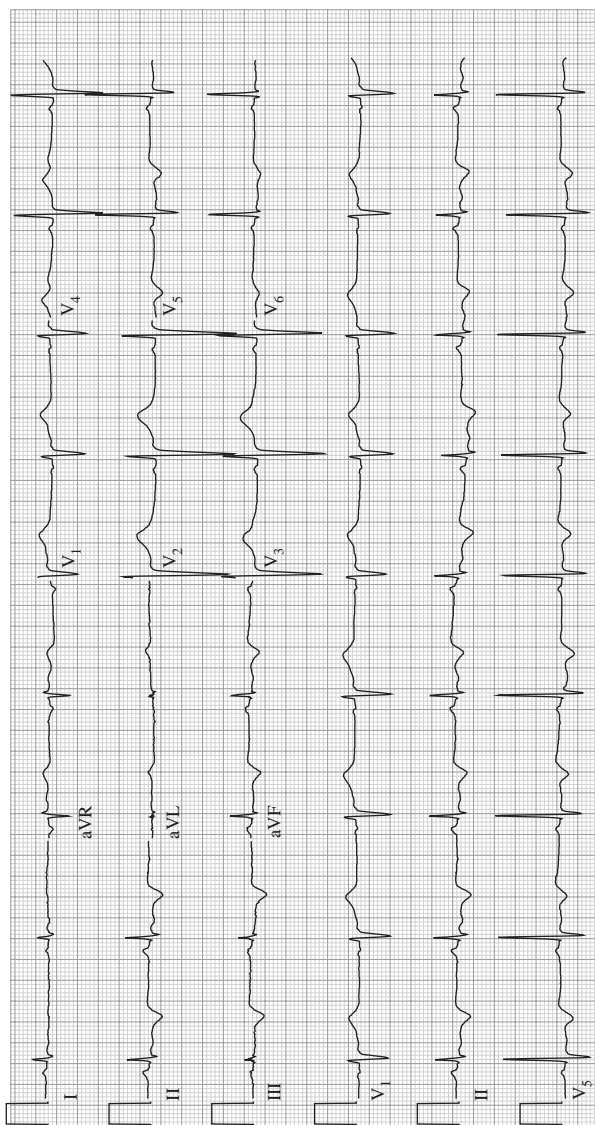


FIGURE 57.20 Hypothermia. Reprinted from Bashian GS, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:588.

- An Osborn or J wave is present at the terminal portion of the QRS complex.
- The QRS interval is prolonged, and there is sinus bradycardia in this example. The PR and QT intervals may also be prolonged.



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FIGURE 57.21 Long QT syndrome.

- The QTc interval is ≥ 440 ms.
- Congenital long QT type I was genetically confirmed in this patient.

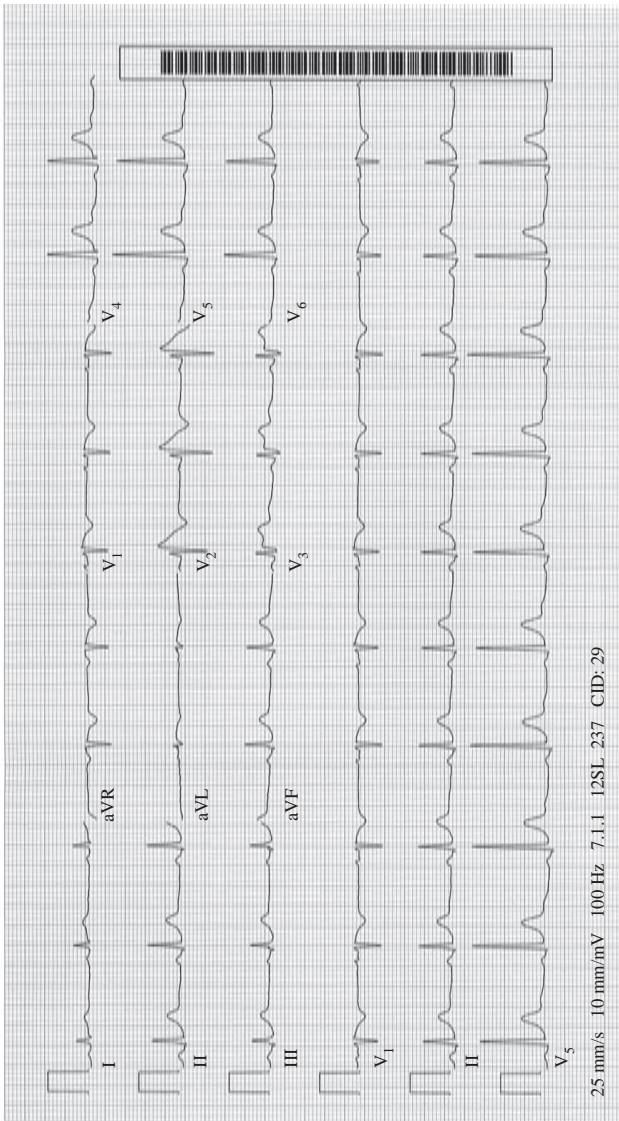


FIGURE 57.22 Type 1 Brugada pattern.

- There is an incomplete RBBB pattern with ST elevation in leads V_1 and V_2 .

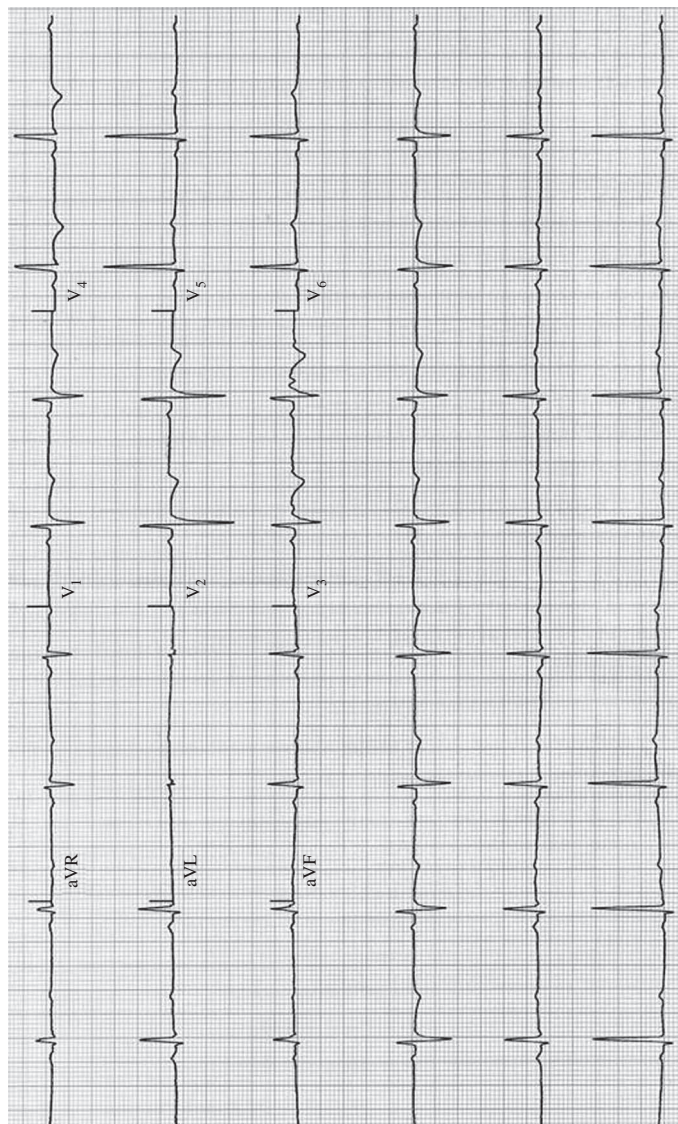
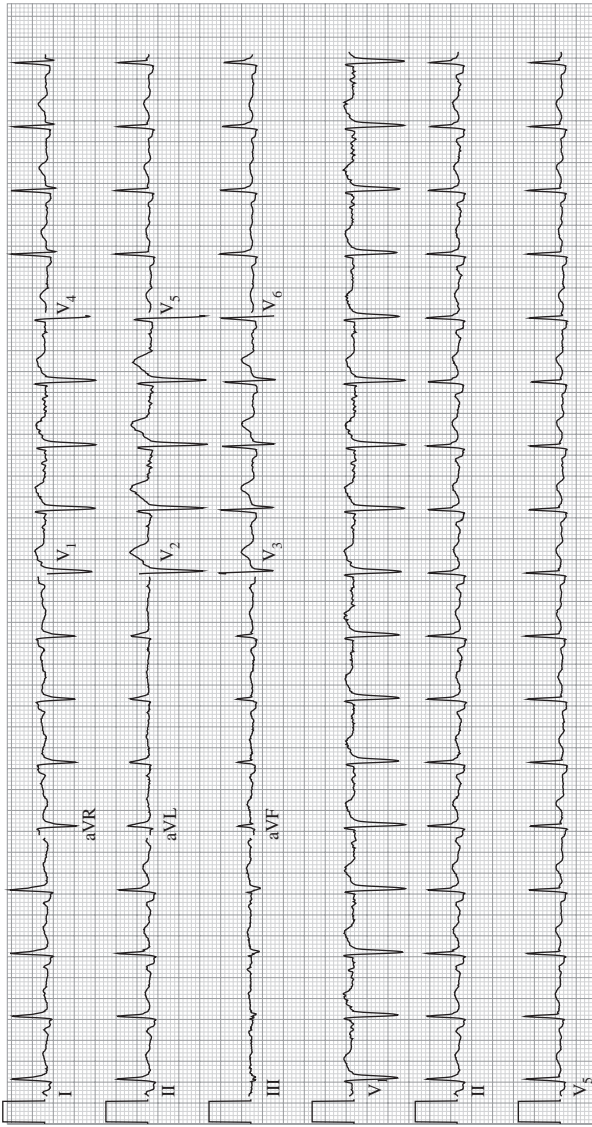


FIGURE 57.23 Arrhythmic right ventricular cardiomyopathy.

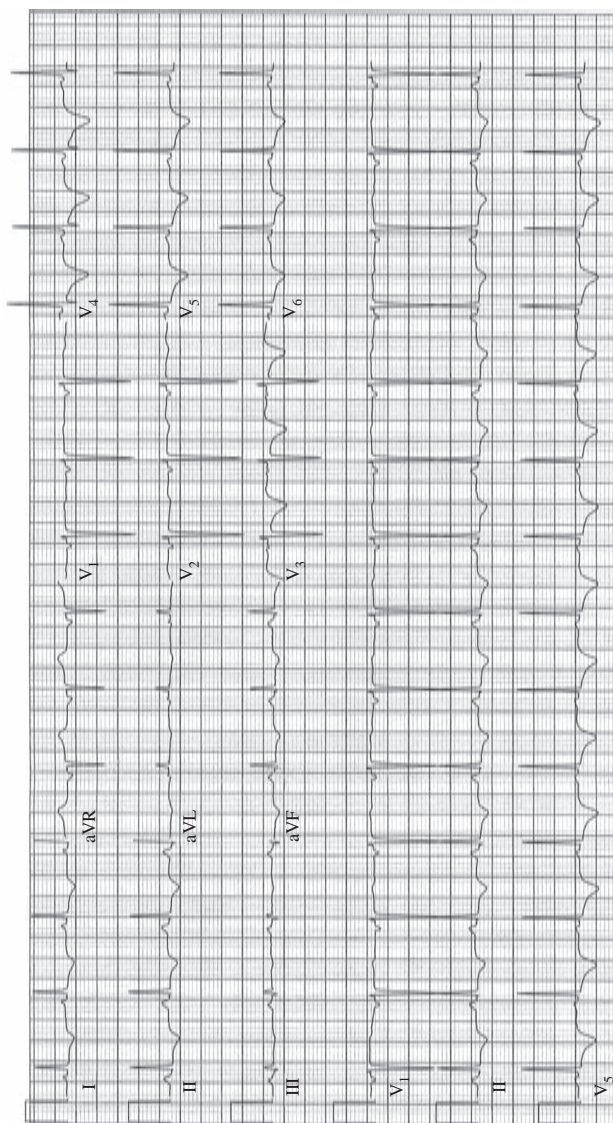
- An epsilon wave is present after the QRS complex in lead V_3 . The epsilon wave may also be seen in leads V_2 and V_3 .
- T-wave inversion in the anteroseptal leads is present.



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FIGURE 57.24 Pericarditis.

- There is diffuse, upwardly concave ST-segment elevation.
- The PR segment is depressed.



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FIGURE 57.25 Takotsubo cardiomyopathy.

- Diffuse ST depression and T-wave inversion are present in this example. ST elevation may also be present.

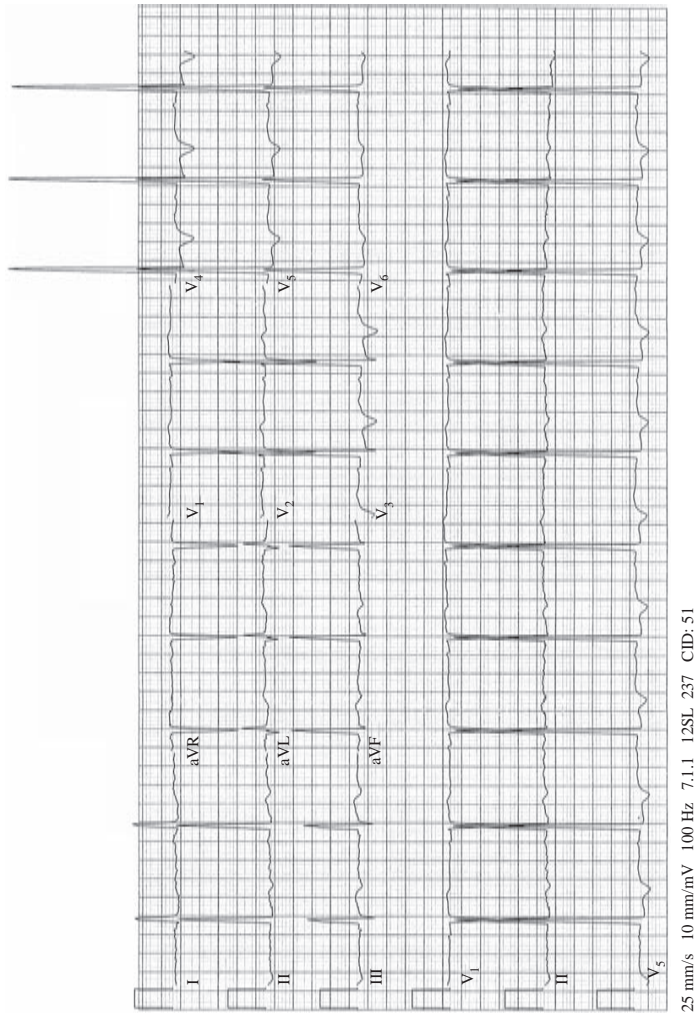


FIGURE 57.26 Apical variant of hypertrophic cardiomyopathy.

- Voltage in the precordial leads is increased and there is anterolateral T-wave inversion.

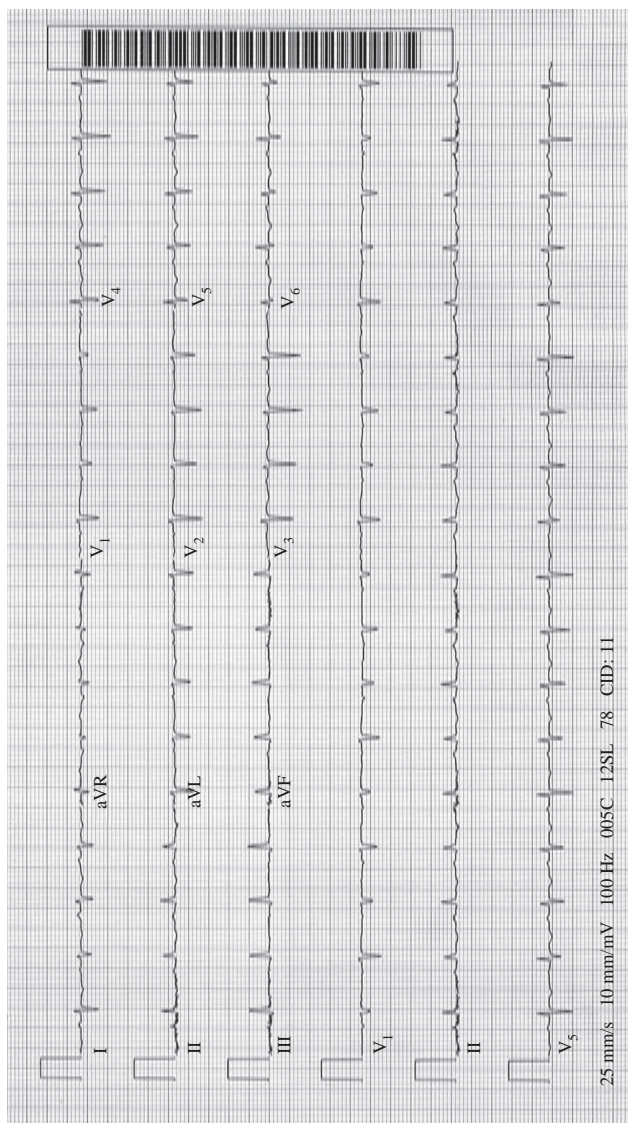


FIGURE 57-27 Pericardial effusion. Reprinted from Bashian GG, Rimmernan CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmernan CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:573.

- Low voltage and electrical alternans are present. This is most apparent in lead V_1 .

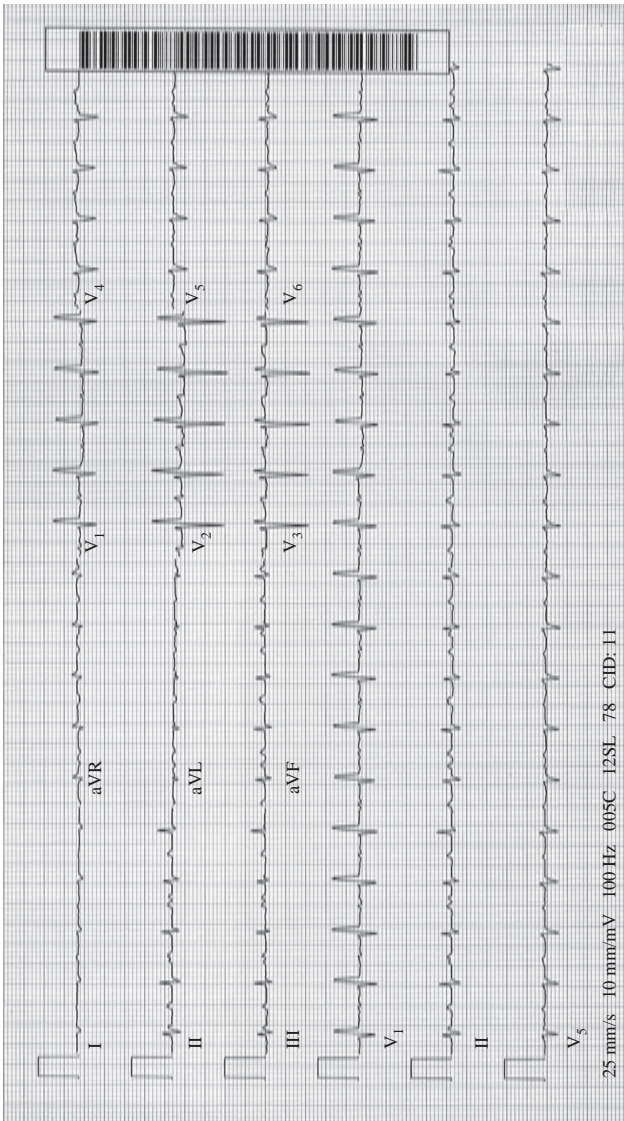


FIGURE 57.28 Cardiac transplant. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:541.

- Two sets of P waves, one from the native right atrium and one from the donor heart, are visible.
- Incomplete RBBB and first-degree AV block are also present.

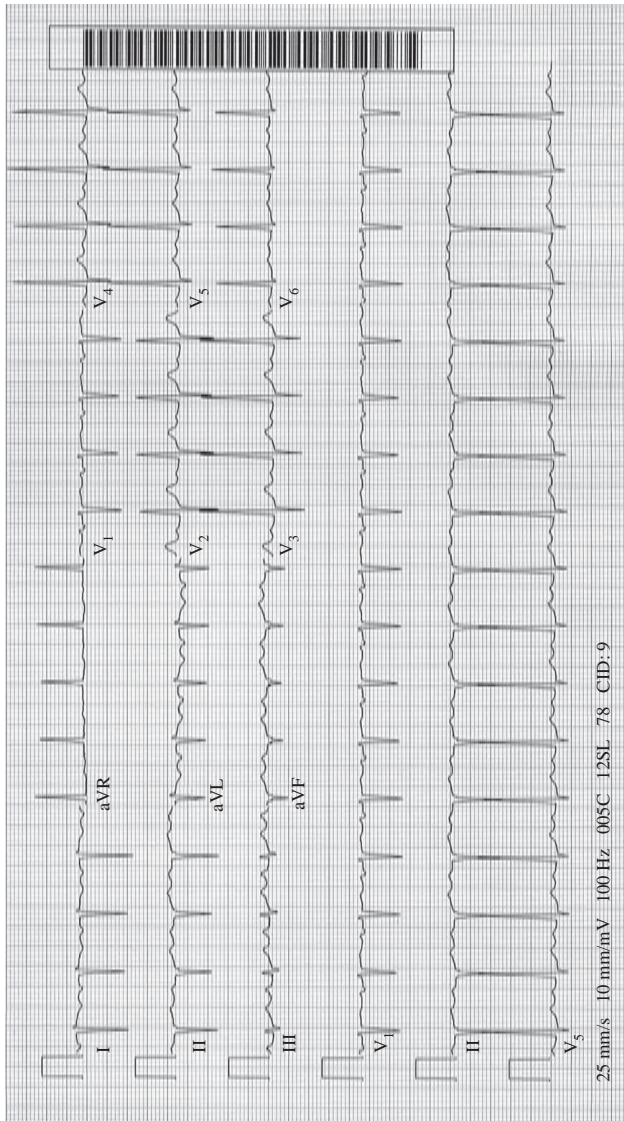


FIGURE 57.29 Limb lead reversal. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:555.

- The QRS complex is negative in lead I, with normal R-wave progression.
- The P wave is negative in leads I and aVL.

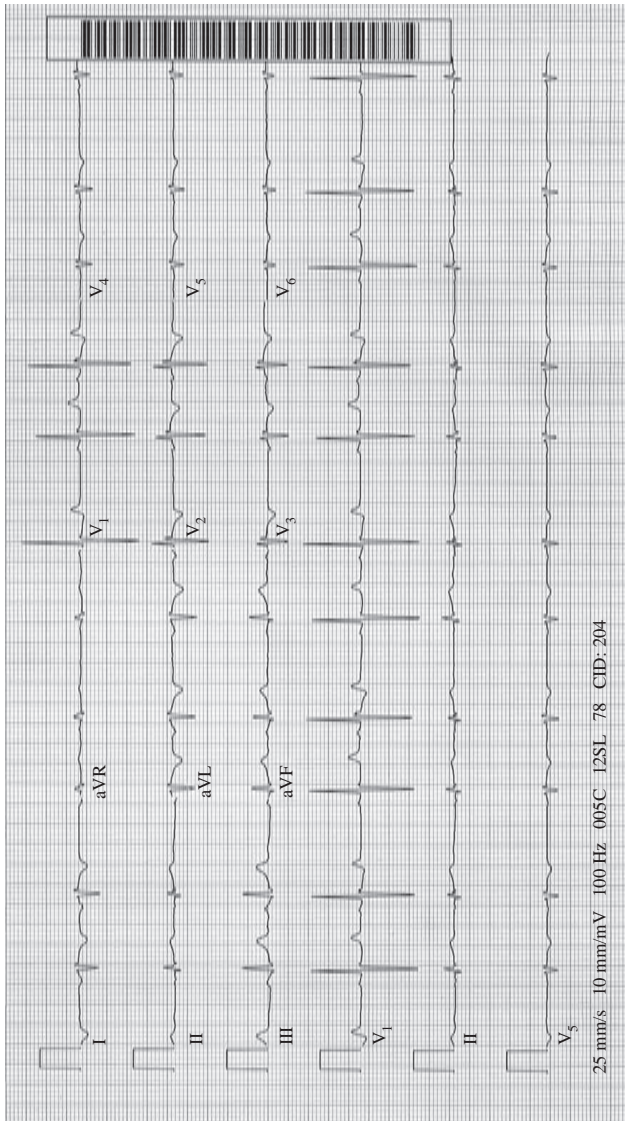


FIGURE 57.30 Dextrocardia. Reprinted from Bashian GG, Rimmerman CM. Twelve-lead electrocardiography. In: Griffin BP, Rimmerman CM, Topol EJ, eds. *The Cleveland Clinic Cardiology Board Review*. Philadelphia, PA: Lippincott Williams & Wilkins; 2007:556.

- The QRS complex is negative in lead I, with R-wave regression across the precordium.
- The P wave is negative in leads I and aVL.
- A premature atrial complex is also present.

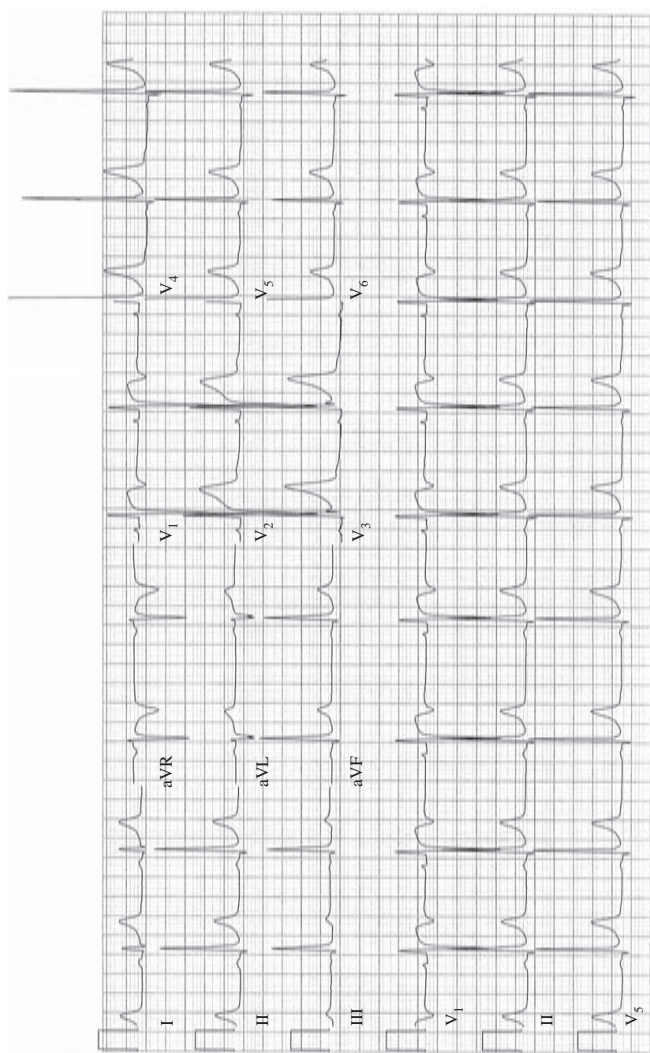


FIGURE 57.31 Early repolarization.

- This electrocardiogram from a young, well-trained athlete shows J-point elevation, concave ST-segment elevation, and large symmetrical upright T waves.
- There is a notch in the downstroke of the R wave.

Temporary Cardiac Pacing

I. INDICATIONS

- A. Acute hemodynamically significant bradycardia or asystole.** Temporary pacing is indicated in patients with acute hemodynamically significant bradycardia or asystole. Reversible causes such as digitalis toxicity, antiarrhythmic agents, and electrolyte disturbances such as hyperkalemia should be determined and reversed.
- B. Termination of tachycardias (overdrive pacing).** Temporary pacing is indicated for overdrive pacing and termination of atrial flutter (type I with long excitable gap) or supraventricular tachycardia due to a reentrant mechanism.
- C. Bridge to permanent pacing.** Temporary pacing may be used as a bridge to permanent pacing in patients with complete heart block, high-grade second-degree block, severe sinus node dysfunction, and asystole. Generally, temporary pacing in this setting is for patients with an acute illness (endocarditis and systemic infection elsewhere) that delays permanent pacemaker placement.
- D. Ventricular tachycardia.** Temporary pacing is indicated in patients with bradycardia-dependent ventricular tachycardia and recurrent tachyarrhythmias secondary to long QT syndrome or pause-dependent ventricular tachycardia. Monomorphic ventricular tachycardia can be terminated with antitachycardia pacing through a ventricular temporary wire by pacing at a rate faster than the tachycardia. This involves pacing the chamber in which the reentrant circuit exists. Overdrive pacing is initiated at 10 to 15 beats per minute (bpm) faster than the tachycardia. Pacing is done for several captured beats (up to 10 to 15 seconds) and then abruptly stopped. If tachycardia persists, the pacing rate is sequentially increased by 10 bpm and pacing repeated. The major potential complication of this technique is conversion to a faster or unstable rhythm. The advantage is that post-tachycardia pauses can be managed with pacing if necessary, and direct current cardioversion may be avoided.
- E. Acute myocardial infarction.** Indications for temporary pacing in this setting include development of a new bifascicular block (right bundle branch block [RBBB] with either left-axis [left anterior hemiblock] or right-axis deviation [left posterior hemiblock]), new left bundle branch block (LBBB) with first-degree atrioventricular (AV) block, alternating LBBB and RBBB, Mobitz type II block, and complete heart block. Patients with right ventricular infarction and loss of AV synchrony may benefit from AV sequential pacing.
- F. Condition where there is a chance of recovery.** In certain forms of myocarditis with heart block, such as Lyme disease, or post cardiac surgery, temporary pacing can be used because there is a significant chance of recovery of conduction.
- G. Acute aortic regurgitation.** Pacing to increase heart rate in patients with acute aortic regurgitation who have bradycardia and elevated left ventricular end-diastolic pressure can reduce diastolic filling time and improve hemodynamics.
- H. Prophylactic.** Prophylactic temporary pacing is considered in the following settings:
 - (a) in patients undergoing right heart catheterization and/or myocardial biopsy in the

setting of an LBBB, (b) with complex intervention to the right coronary artery as this supplies the AV node in 90% of individuals, (c) cardioversion in patients with the sick sinus syndrome, although generally the use of transcutaneous pacing back up is used instead, (d) or new 1st degree AV block with acute endocarditis (especially of the aortic valve). Patients who are undergoing alcohol septal ablation for hypertrophic cardiomyopathy receive prophylactic transvenous pacers, given the significant risk of complete heart block during the procedure. Patients who are undergoing balloon aortic valvuloplasty and percutaneous aortic valve replacement have a temporary pacemaker placed for overdrive pacing during balloon inflation and valve implantation.

- I. **Electrophysiologic studies.** Temporary atrial, coronary sinus, and ventricular pacemakers are frequently used for electrophysiologic studies.
- J. **Ischemic evaluation.** Ischemic evaluation is occasionally performed via rapid atrial pacing.

II. PACING MODES

- A. **Transcutaneous pacing.** Transcutaneous ventricular pacing involves placement of large-surface-area, high-impedance electrodes (Zoll pads) on the anterior (over lead V_3 or the palpable cardiac apex) and posterior chest walls (inferior aspect of the scapula, to the left or right of the spine). It usually requires long pulse widths (20 to 40 milliseconds) and high outputs of up to 100 to 200 mA. Transcutaneous pacing may be useful when transvenous pacing is contraindicated and in code situations. It avoids the complications associated with transvenous pacers such as pneumothorax, right ventricular perforation, infection, bleeding, and venous thrombosis. Failure to capture and severe patient discomfort are common.
- B. **Transesophageal or transgastric pacing.** This technique uses a flexible electrode on the tip of a catheter that is advanced down the esophagus to a position just behind the left atrium and is usually successful in achieving atrial pacing. The electrode can also be advanced to the fundus of the stomach to pace the ventricle through the diaphragm. However, ventricular pacing is difficult to achieve consistently and without intolerable pain to the patient.
- C. **Epicardial pacing.** Temporary epicardial pacing wires are typically placed at the time of valve surgery, given that there is a 6% rate of need for pacemaker prior to discharge in this population, as compared to 0.8% in the setting of coronary artery bypass grafting. Longer cross-clamp time, multiple valve surgical procedure, absence of preoperative sinus rhythm, and reoperation are all predictors of the need for pacemaker implantation in the valvular surgery population. The electrodes are typically removed with gentle traction when they are no longer needed or no longer functional.
- D. **Transvenous pacing**
 1. Relative contraindications
 - a. Poor vascular access
 - b. Bleeding disorders or anticoagulant therapy. If the international normalized ratio is >1.8 and platelets are $<50,000$, then these conditions should be corrected prior to placement of a transvenous pacer if possible.
 2. Patient preparation
 - a. Informed consent should be obtained for the procedure. However, if the patient is hemodynamically unstable because of a cardiac arrhythmia that could be improved with a pacemaker, this procedure is indicated emergently.
 - b. If the procedure is elective, peripheral intravenous access should be obtained before the start of the procedure.
 - c. The procedure should be performed in a monitored setting that is equipped for cardiopulmonary resuscitation and with fluoroscopy being available.
 3. Technique
 - a. **Lead choice.** There is some evidence that active fixation leads allow for greater pacemaker stability and fewer complications than passive fixation

leads. However, active fixation leads can be technically more challenging to place.

- b. **Sites.** The preferred site for pacemaker insertion is the right internal jugular vein. The subclavian vein, femoral vein, and external jugular vein can also be used. However, if a permanent pacemaker will eventually be inserted, the subclavian vein site ipsilateral to the planned permanent pacemaker site should be avoided, if possible. The easiest access in the catheterization laboratory is usually the femoral vein.
- c. **Position.** The patient should be placed supine in bed. The patient may be placed in the Trendelenburg position for internal jugular and subclavian vein cannulation.
- d. **Placement**

(1) **Ventricular pacing.** A venous sheath is inserted into one of the central veins, and pacing catheters are used. When using passive fixation leads, the pacing catheter is advanced through the venous sheath under fluoroscopic guidance (usually 20° to 30° left anterior oblique projection). The catheter is advanced to the tricuspid valve and turned either clockwise or counterclockwise to direct the tip anteriorly. An attempt is made to cross the valve directly. If unsuccessful, gentle pressure is applied and the catheter is torqued, allowing the middle portion to prolapse across the valve into the right ventricle. If the tricuspid valve is difficult to traverse, it may be possible to enter the right ventricle by looping the tip of the catheter against the lateral atrial wall and then rotating the loop medially (counterclockwise) toward the septum. Another option is to reshape the catheter manually, increasing the tip bend before attempting to traverse the tricuspid valve. Once the catheter has entered the right ventricle, it is rotated so that the tip points inferiorly to the apex with minimal movement in systole. The lead can also be advanced into the right ventricular outflow tract, then slowly pulled back until it drops, and then advanced into the apex as it drops. Some degree of buckling is acceptable; however, excessive buckling increases the risk of perforation. Ideally, the pacemaker tip should be near the apex of the right ventricle. The ideal catheter placement site is on the diaphragmatic surface or “floor” of the right ventricle anywhere between its midpoint and its apex. The floor of the more proximal ventricle is a second choice; the true apex is not a good choice for placement of the catheter tip. The paced electrocardiogram from this location usually shows an LBBB pattern with left-axis deviation. Ventricular pacing can also be done with the tip in the right ventricular outflow tract if the catheter cannot be placed on the floor of the right ventricle in a stable position. The pacer tip is considerably less stable at this site compared with the right ventricle floor and is more likely to be displaced; however, this is a very good position for a screw-in temporary pacing wire. Pacing from this location will show an LBBB pattern with an inferior axis. Use of a balloon-tipped temporary pacing electrode can aid in the advancement of the electrode into the proper position. In addition, echocardiographic guidance can be used to help guide lead placement in situations where fluoroscopy is not available or advisable (e.g., pregnant women).

(2) **Atrial pacing.** The right atrium is the easiest chamber to reach and pace, but the most stable position is usually found in the right atrial appendage. For atrial pacing, a J-tipped atrial pacing catheter is used. Alternatively, a temporary screw-in lead can be placed in a stable position with good pacing and sensing thresholds. The atrial appendage is directed anteriorly above the tricuspid annulus, and multiple planes are

frequently helpful in verifying the location. (The catheter appears as a “J” in the left anterior oblique projection or as an “L” in the right anterior oblique projection.)

- (3) Both atrial and ventricular pacing may be performed by placing the catheter in the coronary sinus. The coronary sinus in its proximal portion courses along the left atrium. Ventricular pacing may be achieved by positioning the catheter in a cardiac vein off the coronary sinus. The threshold in the coronary sinus is frequently high, but sometimes it may be a more stable location for atrial pacing than the atrial appendage. Steerable electrophysiologic pacing catheters may be useful in such patients.
- (4) For patients who need extended temporary pacing (those with pacemaker infections or Lyme disease), a permanent pacing wire can be placed in the appropriate chamber percutaneously and sutured to the skin. This can be connected to a temporary pulse generator. In addition, it can be attached to a resterilized permanent device that can be secured to the skin as well. This leads to a very stable intermediate-term pacing system.
4. **Testing.** Once a catheter is in a stable position, threshold testing should be performed. The distal electrode on the pacing catheter is used as the cathode and connects with the negative terminal, and the ring is used as the anode and connects with the positive terminal of the generator. The pacing catheter is attached via a cable to the pacemaker generator.
 - a. **Pacing capture threshold.** Pacing is started at a rate 10 to 20 beats faster than the intrinsic rate with 5 mA output. If capture is not seen at this point, the catheter needs to be repositioned. Once capture is seen, the output is slowly decreased until loss of capture is seen. The lowest capturing current is the pacing *stimulation threshold*. If the catheter is in good position, the threshold should be < 1 mA. Pacing output should be three times the threshold, but pacing is usually performed at a minimum of 5 mA (even if three times the threshold is < 5 mA). This is because minor dislodgment can cause major changes in threshold and adds a safety margin.
 - b. **Sensing threshold.** This is the degree to which the pacemaker sees native cardiac signals (in millivolts). Set the pacing rate to at least 10 bpm below the patient's intrinsic rate. The sensing setting is then gradually decreased until asynchronous pacing is seen. The pacer is set at one-half the sensing threshold.
 - c. **AV interval.** For dual-chamber pacing, the AV interval will need to be programmed. A default of 150 milliseconds is frequently used, but the optimal AV delay may be different in individual patients. Patients with diastolic ventricular dysfunction may need longer AV delay for ventricular filling. In patients with marginal cardiac reserve, obtaining cardiac output measurements at various AV intervals and heart rates may help determine the optimal AV interval and heart rate.
5. **Post-placement chest radiography.** A postprocedure chest radiograph must be evaluated for pneumothorax. For right ventricular apex pacing, in the postero-anterior view, the electrode tip should be located to the left of the spine. In the lateral view, the electrode tip should be directed inferiorly and anteriorly. For pacing through the coronary sinus, the tip is to the left of the spine, directed posteriorly and superiorly.
6. **Pacer care**
 - a. Check the catheter insertion site daily for signs of infection and apply a new sterile dressing at regular intervals.
 - b. Obtain a daily 12-lead surface electrocardiogram, ideally with and without pacing, to assess changes in native conduction and appropriate pacemaker sensing and capture.

- c. Check pacemaker function daily by determining the sensing and pacing threshold, and check the underlying rhythm daily by decreasing the pacing rate gradually to “off.” Abrupt termination in pacing may increase the risk of long pauses.
- 7. Complications**
- a. Related to central venous access such as hematoma at the puncture site, pneumothorax, hemothorax, air embolism, thrombosis, inadvertent arterial puncture, arteriovenous fistula, thoracic duct injury, subcutaneous emphysema, brachial plexus injury, venous thrombosis, and infection.
 - b. Lead dislodgment, particularly with passive fixation leads.
 - c. Cardiac arrhythmias such as premature ventricular contractions, premature atrial contractions, ventricular tachycardia, and RBBB. These are usually of no consequence (although the latter can result in complete heart block in the setting of a preexisting LBBB).
 - d. Myocardial perforation with cardiac tamponade. The unipolar recording from the tip normally shows pronounced ST elevation in comparison with the proximal electrode. ST depression from the tip is associated with perforation. If perforation is suspected, an echocardiogram should be obtained immediately to assess for pericardial effusion. Even a very small pericardial effusion can cause hemodynamic collapse. If pre/tamponade is suspected, emergency pericardiocentesis should be performed. If perforation is suspected and the patient is hemodynamically stable, the temporary pacemaker should be withdrawn only when the physician has all equipment available and is prepared to perform an emergency pericardiocentesis.
 - e. Pacemaker dysfunction with generator failure, oversensing or undersensing, and electrode displacement with failure to capture.
 - f. Complete heart block in patients with preexisting LBBB caused by catheter irritation of the right bundle.

SUGGESTED READING

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- Hayes DL, Zipes DP. Cardiac pacemakers and antiarrhythmic devices. In: Braunwald E, ed. *Heart Disease: A Textbook of Cardiovascular Medicine*. 8th ed. Philadelphia, PA: WB Saunders; 2008:831–862.
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Electrical Cardioversion

- I. **INTRODUCTION.** Delivery of electrical countershock to terminate cardiac arrhythmias is a safe and effective technique that is routinely performed in most hospitals. *Cardioversion* is defined by delivery of energy synchronized to the QRS complex, whereas random delivery of shock during the cardiac cycle (usually done for terminating ventricular fibrillation) is termed *defibrillation*.
- II. **MECHANISM.** Although it has long been recognized that application of an electrical shock to the myocardium can restore a normal rhythm, knowledge of the fundamental mechanism underlying defibrillation remains incomplete. A rapidly delivered electric shock depolarizes the myocardial cells and creates a zone of myocardium with an extended refractory period. Activation fronts encountering tissue with a prolonged refractory period will not be able to propagate, thus terminating both macro- and micro-reentrant circuits. Atrial fibrillation and ventricular fibrillation are generally agreed to be more electrically stable rhythms and thus require higher current delivery for termination. This is likely because only regional depolarization in the path of an advancing wave front is required. The most common waveform shapes used in external defibrillation are the monophasic and biphasic waveforms. In biphasic waveforms, the polarity at each electrode reverses partway through the defibrillation waveform. The use of a biphasic waveform in cardioversion and defibrillation has been shown to be associated with an increased efficacy and may reduce the development of postshock arrhythmias.
- III. **INDICATIONS AND CONTRAINDICATIONS.** The indications and contraindications of cardioversion are listed in Tables 59.1 and 59.2. **Cardioversion should not be performed in patients in whom the rhythm is sinus or the abnormal rhythm is secondary to increased automaticity (e.g., multifocal atrial tachycardia and junctional tachycardia).** If the presenting rhythm is ventricular fibrillation or ventricular tachycardia with hemodynamic compromise, the only clear contraindication to defibrillation is clear expression of the patient's (or patient's surrogate's) informed wish not to be resuscitated.
- IV. **PROCEDURE**
 - A. **Patient preparation**
 1. **Informed consent** should be obtained from the patient or surrogate (if the patient is unable to comprehend and give meaningful informed consent).
 2. In elective cases, patient should **fast for a minimum of 6 to 8 hours**.
 3. A review of the patient's medical **history and a focused physical examination** should be performed. **Special attention should be paid to the airway.** Inability to visualize the uvula, inability to open the mouth with at least 2 cm between the teeth, or difficulty in extending the neck are factors that may make potential

TABLE 59.1 Indications and Contraindications of Cardioversion**INDICATIONS****Cardioversion**

1. Atrial fibrillation/atrial flutter
 - a. Patient with atrial fibrillation/atrial flutter > 48 h (or unknown) duration and anticoagulation for > 3–4 wk (INR 2–3)
 - b. Acute-onset atrial fibrillation/flutter with associated hemodynamic compromise
 1. Angina pectoris
 2. Myocardial infarction
 3. Pulmonary edema
 4. Hypotension
 5. Heart failure
 - c. Atrial fibrillation/flutter of unknown duration and absence of thrombus in left atrium or left atrial appendage on biplane transesophageal echocardiogram
 - d. Atrial fibrillation/flutter < 48 h duration → anticoagulation optional—depending on risk
2. Atrial tachycardia
3. Atrioventricular nodal reentrant tachycardia
4. Reentry tachycardias associated with Wolf-Parkinson-White syndrome
5. Ventricular tachycardia

Defibrillation

1. Ventricular fibrillation
2. Ventricular tachycardia with hemodynamic instability

CONTRAINDICATIONS**Cardioversion**

1. Known atrial thrombus and no emergent indication
2. Sinus rhythm/tachycardia
3. Tachycardias associated with increased automaticity
 - a. Multifocal atrial tachycardia
 - b. Junctional tachycardia
4. Digitalis toxicity
5. Severe electrolyte imbalance and nonemergent indication
6. Unknown duration of atrial fibrillation or atrial flutter in a nonanticoagulated patient in the absence of transesophageal echocardiogram
7. Patient who cannot be safely sedated

Defibrillation

1. Prior expression of patients who wish not to be resuscitated

INR, international normalized ratio.

intubation difficult and may suggest the need for the presence of an anesthesiologist during the procedure.

4. The patient's **medication and anticoagulation status** (for patients in atrial fibrillation or flutter) should be confirmed. Because patients may not always have symptoms with arrhythmias such as atrial fibrillation and atrial flutter, convincing historical or electrocardiographic evidence of the tachycardia initiating within 48 hours of cardioversion should be documented before cardioverting a patient with atrial fibrillation or atrial flutter without adequate anticoagulation due to the risk of thromboembolism.

TABLE 59.2 **Indications for Cardioversion in Patients with Atrial Fibrillation****Class I**

1. Immediate electrical cardioversion in patients with paroxysmal AF and a rapid ventricular response who have electrocardiographic evidence of acute MI or symptomatic hypotension, angina, or HF that does not respond promptly to pharmacologic measures.
2. Cardioversion in patients without hemodynamic instability when symptoms of AF are unacceptable.

Class IIa

1. Electrical cardioversion to accelerate restoration of sinus rhythm in patients with a first-detected episode of AF.
2. Electrical cardioversion in patients with persistent AF when early recurrence is unlikely.
3. Repeated cardioversion followed by prophylactic drug therapy in patients who relapse to AF without antiarrhythmic medication after successful cardioversion.

Class III

1. Electrical cardioversion in patients who display spontaneous alteration between AF and sinus rhythm over short periods of time.
2. Additional cardioversion in patients with short periods of sinus rhythm who relapse to AF despite multiple cardioversion procedures and prophylactic antiarrhythmic drug treatment.

AF, atrial fibrillation; HF, heart failure; MI, myocardial infarction.

Adapted from ACC/AHA/ESC 2001 guidelines.

5. **Anticoagulation** is a key factor for patients in atrial fibrillation or flutter (Table 59.3) to prevent thromboembolism. The two key oral anticoagulants that may be used for anticoagulation are Coumadin and the newly approved dabigatran, which is used for nonvalvular atrial fibrillation or flutter. Therapeutic levels of anticoagulation for Coumadin and dabigatran differ in timing. For Coumadin, there is frequent laboratory monitoring that needs to be done with adjustment of dosing to reach a target international normalized ratio of 2 to 3, which on average takes 3 to 5 days. However, in regard to dabigatran, there is no laboratory monitoring needed, with therapeutic levels being achieved in about 12 hours. The dosing is fixed at 150 mg bid for patients with creatinine clearance (CrCl) > 30 mL/min and 75 mg bid with CrCl of 15 to 30 mL/min.
 6. A 12-lead electrocardiogram (ECG) should be obtained to **confirm the presenting rhythm**, as well as to discern any suggestion of electrolyte abnormality (hypo- or hyperkalemia) or drug toxicity (digitalis). If any of these is suspected, appropriate blood levels should be checked. Routine measurement of digoxin levels is not recommended.
 7. **Peripheral venous access** should be obtained for elective cases.
 8. A good-quality **continuous ECG** should be obtained. Good contact of the skin and electrodes is essential, and proper skin preparation, including shaving of the chest hair (if present), is recommended.
 9. **Oxygen and airway management** equipment (including suction with suction catheters, bag valve mask, laryngoscope, endotracheal tubes, and pulse oximeter) is required and should be checked prior to the procedure.
- B. Technique**
1. Once the patient is adequately prepared and an appropriately trained physician is present, **cardioversion patches are placed and the patient is sedated**.

TABLE 59.3 Anticoagulation Status and Cardioversion for Atrial Fibrillation/Flutter**Anticoagulation before cardioversion**

1. Administer oral anticoagulation with Coumadin and ensure therapeutic INR (> 2) or dabigatran (no need for laboratory monitoring) for nonvalvular atrial fibrillation/flutter for a minimum of 3–4 wk prior to cardioversion (target INR 2–3)

or

2. Anticoagulate with heparin^a to achieve a PTT 1.5–2 times control and screen for thrombus in left atrium or left atrial appendage by transesophageal echocardiography
 - a. If no thrombus, cardiovert and continue heparin while loading Coumadin or dabigatran. In regard to Coumadin, continue the heparin until INR is therapeutic (≥ 2). If dabigatran is used, it would be reasonable to continue heparin until anticoagulation status is therapeutic, which is about 12 h

or

- b. If thrombus is visualized, anticoagulate for 3–4 wk with either Coumadin (target INR 2–3) or dabigatran and recheck transesophageal echocardiogram to confirm thrombus is resolved prior to cardioversion
3. If emergent indication

Administer heparin (unless contraindicated) to achieve PTT 1.5–2 times control prior to or immediately after cardioversion

Anticoagulation after cardioversion

Oral anticoagulation for at least 4 wk with Coumadin for a target INR 2–3 or dabigatran if no contraindications

^aLimited data support the use of low-molecular-weight heparin (LMWH) before or after cardioversion (level of evidence: C). Use of LMWH in such clinical situations must be individualized after careful determination of the risks and benefits involved.

INR, international normalized ratio; PTT, partial thromboplastin time.

2. **Electrode placement.** Electrode placement on the chest is important to maximize current flow through the heart, which is what actually terminates the arrhythmia. Patches or paddles may be placed in the anteroapical or the antero-posterior position.
 - a. Although the anteroapical position is easy to use in an emergency, it is associated with a lower delivery of current to the myocardium.
 - b. The left anteroposterior position is commonly used for cardioversion of atrial arrhythmias because it is associated with a smaller interelectrode distance and a lesser interposition of lung parenchyma. This enhances delivery of current to the atria and improves the success of cardioversion.
 - c. The right parasternal–left paravertebral electrode patch position is associated with better current delivery to both atria and is particularly useful in patients with atrial abnormalities (e.g., atrial septal defect and rheumatic valve disease). This electrode position is favored in our laboratory for cardioversion of atrial fibrillation (Fig. 59.1).
 - d. Although internal cardioversion (using a right atrial catheter and a coronary sinus catheter as electrodes or using a right atrial and a posteriorly placed external electrode) has been used in the past for cardioverting morbidly obese patients or patients who are resistant to external cardioversion,

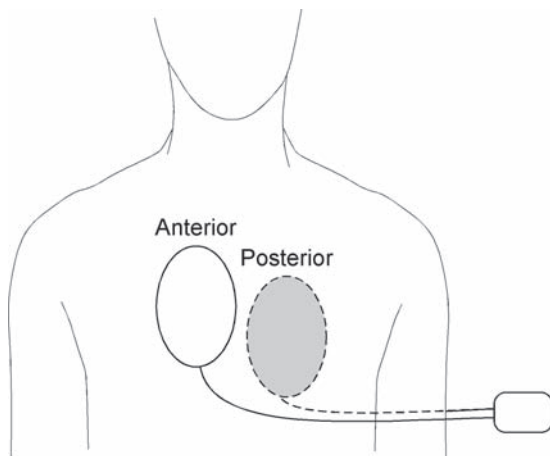


FIGURE 59.1 Right parasternal–left paravertebral electrode patch position.

it is now rarely necessary, given the widespread availability of biphasic cardioversion.

3. **Sedation.** Short-acting sedatives should be administered before all elective cardioversions, since the procedure is uncomfortable. Commonly used agents include methohexital (0.5 to 0.6 mg/kg body weight), etomidate (0.2 to 0.6 mg/kg body weight over 30 to 60 seconds), propofol (0.7 to 1.2 mg/kg, followed by 0.5 mg/kg every 3 to 5 minutes as needed), and midazolam (0.5 to 2 mg over 2 minutes, repeated every 2 to 3 minutes if necessary). Adequate sedation is confirmed by lack of response to verbal and pressure stimuli and loss of eyelash reflex. Airway, breathing, and oxygenation should be monitored until the patient makes a complete recovery, and appropriate support is provided as needed.
4. **Energy selection.** Success of cardioversion is dependent on adequate energy delivery to the heart. This in turn is dependent on the energy output, current vector, and the transthoracic impedance.
 - a. The commonly used energy selection for various arrhythmias is outlined in Table 59.4. The energy selected differs between monophasic and biphasic devices.
 - b. Impedance is defined as opposition to electrical flow or current. Higher impedance results in a reduction in current delivery to the myocardium. Therefore, initial energy selection should be individually tailored after consideration of important patient factors such as body habitus and the presence of lung disease, which may affect impedance. In addition, all efforts must be made to reduce impedance. A key factor that modulates impedance is electrode size, with optimal size approximating the size of the heart. Although smaller electrodes increase impedance, larger ones are associated with current wastage. The optimal diameter of an electrode for an adult patient is approximately 12 cm. Other measures to reduce impedance include application of pressure on the electrodes (approximately 12 kg) during shock delivery, shock during end-expiration, better skin–electrode interface and use of conducting gels, and repeat administration of shocks.

TABLE 59.4 Initial Energy Selection for Commonly Encountered Arrhythmias

Arrhythmia	Energy output (J)	
	Monophasic	Biphasic
Ventricular fibrillation (or unstable ventricular tachycardia)	200	120
Atrial fibrillation	200	100
Atrial flutter	50	50
Supraventricular tachycardia	150	100
Ventricular tachycardia (stable)	100	50–100

Conversely, increasing interelectrode distance and interposition of soft tissue or pulmonary parenchyma increases impedance.

5. **Synchronization.** Once the underlying rhythm is confirmed and a good-quality ECG is obtained, the synchronize mode is switched on (except for defibrillation where mode must be asynchronous). Synchronization is essential to prevent delivery of shock during the vulnerable period (from 80 milliseconds before to 30 milliseconds after the apex of T wave), with resultant ventricular fibrillation. Defibrillators are designed to time the shock to the R wave during synchronization mode. The position of the timing artifact on the R wave is confirmed on the monitor and on a printout, because the defibrillator may rarely synchronize to the T wave. Conversely, when defibrillating, the mode must be asynchronous because lack of identifiable QRS complex prevents a defibrillator in the synchronous mode from discharging.
6. **Delivery of shock.** Once the patient is adequately prepared, the electrodes are adequately positioned, and the appropriate output and mode are selected, the adequacy of sedation should be reconfirmed. The defibrillator capacitors are charged, the ancillary staff are warned to stay clear of the patient, proper synchronization is reconfirmed, and the appropriate shock is delivered. The patient is immediately assessed for adequacy of airway, breathing, and circulation. The ECG is inspected to confirm rhythm, and if sedation is still adequate, the procedure is repeated if necessary. The patient is monitored until complete recovery (generally 1 hour). Anticoagulation and antiarrhythmic medications (if any) must be addressed before discharge.

V. COMPLICATIONS OF CARDIOVERSION.

Complications after cardioversion are uncommon but include the following.

- A. **Thromboembolism.** About 1% to 7% of patients in atrial fibrillation not anticoagulated before cardioversion develop arterial embolization after the procedure. In appropriately anticoagulated patients, the incidence of embolism is extremely low. In the Assessment of Cardioversion Using Transesophageal Echocardiography (ACUTE) trial, comparing anticoagulation for 3 weeks before cardioversion to transesophageal echocardiography (TEE)-guided therapy, the incidence of embolism was 0.5% in the conventional arm and 0.8% in the TEE-guided arm. TEE-guided cardioversion is now widely used in patients who require cardioversion urgently but who have not been adequately anticoagulated for 3 weeks.
- B. **Arrhythmias.** It is not uncommon for patients to have premature atrial contractions or premature ventricular contractions after cardioversion. Although

some patients exhibit transient sinus arrest or atrioventricular block, this is usually self-limited. However, the ability to provide emergent temporary transthoracic pacing should be available for the rare patient who needs it. Malignant ventricular tachyarrhythmias are rare but may occur if the shock is delivered during the vulnerable period. The risk of malignant tachyarrhythmias is increased in the setting of hypokalemia or digoxin toxicity.

- C. **Injuries.** The incidence and severity of chest wall burns can be reduced by the use of conductive gel, good skin and electrode contact, and use of lowest effective energy output.
- D. **Airway compromise.** Excessive sedation may be associated with respiratory depression. This is more likely in the elderly or in those with hepatic or renal dysfunction. Appropriate adjustment of dose and monitoring of airway and oxygenation until complete recovery will minimize any undue effects of excessive sedation.
- E. **Myocardial depression.** Cardioversion is a safe procedure with a wide margin of safety. Transient ST-segment elevation without apparent myocardial damage and minor elevations in creatine kinase myocardial band isoenzyme or in troponin I have been reported in rare instances. Rarely, patients have developed pulmonary edema after direct current cardioversion.
- F. **Injuries to the operator.** Injuries to the operator are rare, with an incidence <1 in 1,700 in one series. Most are minor electrical injuries and manifest as extremity paresthesias. Major electrocution is extremely rare, and the reported cases have all been associated with equipment malfunction. Cardioversion in the presence of wet skin or nitroglycerin ointment can lead to arcing and may present a fire hazard.

VI. TROUBLESHOOTING

- A. **Monitor does not work.** This is usually related to a mechanical problem. The power source, lead connections, and monitor lead electrode patches should be checked.
- B. **Timing artifact falls on T wave.** Monitoring lead should be changed and the correct position of the timing artifact confirmed prior to cardioversion.
- C. **Capacitor does not discharge.** When operating in the synchronized mode, the capacitor will not discharge until it recognizes a synchronized QRS. The switch should be pressed until the capacitor discharges. If this method fails, the monitoring lead should be changed and cardioversion attempted again.
- D. **Cardioversion unsuccessful**
 - 1. The first step should be to repeat the ECG to check the underlying rhythm to confirm diagnosis and to differentiate between failure to cardiovert and successful cardioversion that is followed by recurrence of the presenting arrhythmia.
 - 2. For patients who truly fail to cardiovert, a higher energy level may be considered for a repeat attempt. A biphasic device should be used if available and all possible measures to reduce impedance applied (Section IV.B.4.b).
 - 3. Another option for patients who truly fail to cardiovert is to reposition the patches to better capture the myocardium between the patches and, if not done initially, application of pressure on the electrodes (approximately 12 kg) during shock delivery to improve contact and decrease impedance.
 - 4. Unsuccessful cardioversion may be secondary to a deranged metabolic milieu, and reversible causes (such as electrolyte imbalance or thyrotoxicosis) should be corrected.
 - 5. Patients who are on long-term amiodarone therapy may present with atrial fibrillation as the first manifestation of amiodarone-induced hyperthyroidism, which may in turn make cardioversion more difficult.
 - 6. In resistant cases where a biphasic device is unavailable, reversing the polarity of the electrodes with cardioversion at maximal energy, using two defibrillators to increase current, or internal cardioversion may be an option.

7. Use of appropriate antiarrhythmic drugs may facilitate cardioversion and maintenance of sinus rhythm, and the procedure may be repeated after loading with appropriate drugs. Pretreatment with 1 mg ibutilide has been shown to increase the likelihood of successful cardioversion. Ibutilide administration has been associated with the development of torsade de pointes. At our institution, patients pretreated with ibutilide are also given 1 g of IV magnesium sulfate in order to minimize this risk.
8. Predictors of unsuccessful cardioversion in chronic atrial fibrillation include long duration of atrial fibrillation, underlying structural heart disease, left atrial enlargement, and cardiomegaly.

VII. SPECIAL SITUATIONS

A. Preexisting permanent pacemaker or implantable cardioverter-defibrillator.

Electric current can conduct along the implanted electrode lead and cause myocardial injury. This may manifest as a temporary or permanent increase in stimulation threshold, and, when pronounced, this may manifest as failure of capture-exit block. This can be avoided by **positioning electrodes away from the device**; therefore, the anteroposterior position is preferred. The device should be interrogated before and after cardioversion.

B. Pregnancy.

Successful cardioversion has been carried out in all trimesters of pregnancy without ill effects to the mother or the fetus.

VIII. FUTURE DIRECTIONS. A very important area for future improvement in a technique that has changed so little over the last several decades is to reduce the defibrillation thresholds. This could possibly serve to eventually eliminate pain, anesthesia, and sedation during shocks. Current research points to more effective cardioversion/defibrillation waveforms; shocks from ≥ 2 sites simultaneously and combination of shocks with cardiac pacing may prove particularly useful. In regard to the combination of shocks and cardiac pacing, we already know that pacing can influence and terminate reentrant or triggered arrhythmias. As noted in previous work with animal models and humans on the mechanisms of ventricular fibrillation and atrial fibrillation suggesting the presence of one or more drivers that may make this strategy plausible, the goal of this combination would be for less energy to be used to restore normal sinus rhythm.

IX. AUTOMATIC EXTERNAL DEFIBRILLATORS. The automatic external defibrillator is a battery-operated microprocessor-based defibrillator that identifies tachyarrhythmias and, upon activation, delivers a shock to terminate them. This device is designed for use on an unresponsive patient with cardiac arrest. The system includes external self-adhesive pads that are applied on the victim, after which the device is switched on and cardiopulmonary resuscitation temporarily discontinued. The device analyzes the rhythm and advises the operator to press a switch to deliver a nonsynchronized shock, reanalyzes the resulting rhythm, and advises further delivery of shock if indicated. These devices are easy to use and designed to be used in the field by lay people. In various studies, the sensitivity and specificity of detection and success of termination of ventricular fibrillation and ventricular tachycardia have been $> 90\%$, with a significant reduction in the response time for the first shock.

ACKNOWLEDGMENTS: *The author thanks Drs. Hitinder S. Gurm, Robert A. Schweikert, and Thomas Callahan for their contributions to earlier editions of this chapter.*

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Right Heart Catheterization

- I. INTRODUCTION.** In 1947, Dexter et al. (1) observed that the pressure recorded by a catheter wedged in the pulmonary artery (PA) was similar to the filling pressure in the left ventricle. In 1970, Swan and colleagues (2) reported that PA catheterization could be performed at the bedside by using a specially designed balloon-tipped catheter. This landmark observation brought right heart catheterization (RHC) to the bedside and it remains an integral part of the diagnostic armamentarium of the cardiologist. Although the routine use of RHC data to guide treatment in critically ill patients in the intensive care unit has been associated with harm, it remains the gold standard in hemodynamic monitoring, and its use can be crucial in diagnosing and treating critically ill patients with cardiovascular disease.

The utility of hemodynamic variables obtained from RHC as a diagnostic and prognostic marker in patients with acute myocardial infarction (MI), cardiogenic shock, and heart failure (HF) is well established. Proving that a clinical benefit exists for continuous RHC hemodynamic monitoring has, however, been challenging. Retrospective observational analyses on the utility have been limited by patient selection as well as survival biases. In the National Heart Lung Blood Institute–supported ESCAPE (Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness) trial, the utilization of PA catheters was not associated with worse outcomes. In this trial of 433 patients randomized to therapy for class IV HF guided by either clinical assessment or clinical assessment plus PA catheterization, there was no difference in the primary end point of days alive out of the hospital during the first 6 months after hospitalization. There was an increase in in-hospital adverse events in the PA catheter group; however, there were no deaths related to PA catheter use and no difference in in-hospital or 30-day mortality between the two groups.

- II. INDICATIONS AND COMMON USES.** See Table 60.1 for ACC recommendations for using PA catheterization.
- (A) **Acute MI** complicated by hypotension, congestive heart failure, sinus tachycardia, right ventricular (RV) infarction, or mechanical complications (such as ventricular septal defect [VSD], pericardial tamponade, or acute mitral regurgitation [MR]).
 - (B) **Assessment of volume status** in patients in whom physical signs may be unreliable (e.g., morbidly obese or ventilated patients).
 - (C) **Severe left ventricular (LV) failure** to guide inotropic, diuretic, and afterload reduction management.
 - (D) **Differentiation between various shock states** (e.g., cardiogenic, distributive, or hypovolemic) and guidance of therapies.
 - (E) **Risk stratification for patients during heart transplant evaluation.**
 - (F) **Cardiac tamponade.** Although echocardiography is the diagnostic test of choice, PA catheterization may be used when echocardiography is not readily available or nondiagnostic and the risk or difficulty of pericardiocentesis is high.
 - (G) **Assessment of the level and magnitude of an intracardiac shunt,** especially if transthoracic echocardiography is nondiagnostic.

TABLE 60.1 Common Indications for the Use of Right Heart Catheterization
HF

1. To differentiate between cardiogenic and noncardiogenic pulmonary edema.
2. To differentiate between cardiogenic and noncardiogenic shock and to guide its pharmacologic or mechanical support.
3. To guide therapy in patients with biventricular HF.
4. To diagnose pericardial tamponade when echocardiography is unavailable or nondiagnostic.
5. Perioperative management of patients with decompensated HF undergoing high-risk surgery.
6. To identify reversible pulmonary hypertension in patients undergoing heart transplant evaluation.

Acute MI

1. To differentiate between cardiogenic and hypovolemic shock.
2. To guide pharmacologic and/or mechanical support of cardiogenic shock in patients with or without coronary reperfusion therapy.
3. Short-term guidance of pharmacologic and/or mechanical support in acute MR before surgery.
4. To establish severity and for short-term guidance of pharmacologic and/or mechanical support of ventricular septal rupture before surgery.
5. To guide management of right ventricular infarction that does not respond to intravascular volume expansion, low doses of inotropic drugs, and/or restoration of heart rate and atrioventricular synchrony.
6. To manage acute pulmonary edema that does not respond to treatment with diuretics, nitroglycerin, other vasodilators, and/or low doses of inotropic drugs.

Perioperative use in cardiac surgery

1. To determine the etiology of low cardiac output (hypovolemia vs. ventricular dysfunction) when exam and echocardiography are inconclusive.
2. To differentiate between right and left ventricular dysfunction and pericardial tamponade when exam and echocardiography are inconclusive.
3. To guide management of severe low cardiac output syndrome.
4. To diagnose and guide management of pulmonary hypertension in patients with systemic hypotension and evidence of inadequate organ perfusion.

PAH

1. To exclude postcapillary (elevated pulmonary capillary wedge pressure) causes of pulmonary hypertension.
2. To diagnose and establish the severity of precapillary (normal pulmonary capillary wedge pressure) pulmonary hypertension.
3. To select and establish the safety and efficacy of long-term vasodilator therapy based on acute hemodynamic response.
4. For hemodynamic assessment before lung transplantation.

HF, heart failure; MI, myocardial infarction; MR, mitral regurgitation; PAH, pulmonary arterial hypertension.

Adapted from Mueller HS, Chatterjee K, Davis KB, et al. ACC expert consensus document: present use of bedside right heart catheterization in patients with cardiac disease. *JACC*. 1998;32:840–864.

- (H) **Differentiation between constrictive and restrictive cardiac physiology.**
- (I) **Severe pulmonary hypertension (PH).**
- (J) **High-risk cardiac patients during preoperative, intraoperative, and postoperative periods** to monitor volume status and cardiac output (CO).
- (K) **Severe adult respiratory distress syndrome (Noncardiogenic Pulmonary Edema)** during positive end-expiratory pressure trials to assess CO.

III. CONTRAINDICATIONS. The absolute contraindications to PA catheter placement are right-sided endocarditis, a mechanical tricuspid or pulmonic valve prosthesis, thrombus or tumor in a right heart chamber, uncooperative patient, and terminal illness for which aggressive management is considered futile. Relative contraindications are profound coagulopathy (international normalized ratio > 2 or platelet count $< 20,000$ to $50,000$), bioprosthetic tricuspid or pulmonic valve prosthesis, newly implanted pacemaker or defibrillator (unless fluoroscopic guidance is used), and left bundle branch block (LBBB). The latter is a relative contraindication because local trauma to the functioning right bundle while introducing the PA catheter may result in complete heart block and hemodynamic instability. **Consequently, temporary pacing should be immediately available when inserting a PA catheter in patients with preexisting LBBB.** Finally, it would be advisable to treat any pneumothorax/hemothorax on the contralateral lung before proceeding, in the event of an ipsilateral pulmonary injury caused by the procedure.

IV. TECHNIQUE

A. Venous introducer/sheath insertion. It is important to obtain informed consent in plain language from the patient before the procedure, addressing the utility and major complications of PA catheterization (Table 60.2). Once the procedure is ready to commence, a checklist system should be utilized to ensure safety and success, including a time-out process that confirms “right patient, right procedure, and right site of access.” Using a central line kit is a convenient way to streamline the procedure. The patient should be prepped and draped in a sterile fashion from head to toe during the catheter insertion, regardless of the insertion site chosen. Multiple sites can be used for introducer placement; however, **a site that can be readily compressed, such as the internal jugular (IJ) vein, is preferred. Localization and entry into the vein is best performed under ultrasound guidance as an imaging-guided approach decreases procedural complications.** Cannulation of the vein utilizing anatomical landmarks should only be used when ultrasound guidance is unavailable.

TABLE 60.2 **Complications of Right Heart Catheterization**

Related to the introducer	Related to the catheter passage	Related to the catheter
Arterial puncture	Arrhythmia (PVC, NSVT, VF)	Thrombosis
Bleeding from insertion site	Complete heart block or RBBB	Thrombophlebitis
Pneumothorax	Coiling	
Nerve injury/Horner's syndrome	Valve trauma PA/RV perforation	PA infection Bacteremia \pm endocarditis
Air embolism		Balloon rupture \pm embolization

NSVT, nonsustained ventricular tachycardia; PA, pulmonary artery; PVC, premature ventricular contraction; RBBB, right bundle branch block; RV, right ventricular; VF, ventricular fibrillation.

1. The **IJ vein** (see Fig. 60.1) has multiple advantages, such as compressibility and minimal risk of pneumothorax. The disadvantages are the potential for accidental carotid artery puncture and limited neck mobility for patients. The IJ vein can be entered via an anterior or posterior approach. The right side is generally preferred because the vein runs a direct path to the right atrium. Often, it is easier to access the IJ vein if the patient is in the Trendelenberg position. The anterior approach uses the triangle created by the two heads of the sternocleidomastoid muscle and the clavicle. A finger should always be placed on the carotid artery to identify its position and to retract it medially. The needle should be inserted at the apex of this triangle and advanced in the direction of the ipsilateral nipple at a 45° angle. The vein can usually be entered 3 to 5 cm from the skin surface. In order to minimize complications, the vein should be found with a finder needle (20G) before using the large-bore catheter (16G) needle. Once the IJ vein is cannulated, the catheter-over-guidewire approach should be used to place the introducer. The guidewire minimizes damage to the vessel and should pass smoothly. Never force the guidewire. If difficulty in threading the wire is encountered, reattach the syringe and attempt to aspirate venous blood to ensure that the needle tip is still located in the vessel. An instructional video available from the *New England Journal of Medicine* web site (see reference) is a helpful tool for clinicians and students alike.

An alternative IJ vein access is the posterior approach. The advantage of this approach is that it minimizes the risk of carotid artery puncture. First, the external jugular vein is located, and the IJ vein is cannulated 1 cm superior to the point where the external jugular vein crosses the lateral edge of the sternocleidomastoid muscle. Another posterior approach is to puncture along the posterior edge of the sternocleidomastoid muscle, two fingerwidths above the clavicle. The needle should be pointing toward the posterior aspect of the upper portion of the manubrium sterni.

2. **Cannulation of the subclavian vein** (see Fig. 60.1) is associated with greater patient comfort. However, there is an increased risk of pneumothorax and inadvertent subclavian artery cannulation, especially in patients on mechanical ventilation or with chronic obstructive pulmonary disease. The vein lies just under the clavicle at the insertion site for the clavicular head of the sternocleidomastoid muscle. This is where the vein should be cannulated. The subclavian artery lies just beneath the anterior scalene muscle, which is just below the subclavian vein, with the lung just underneath the artery. For better landmark definition and separation of the vein from the pleura, a rolled-up towel can be placed between the scapulae. There are two approaches to cannulating the subclavian vein: infraclavicular and supraclavicular. The infraclavicular approach is used more frequently.

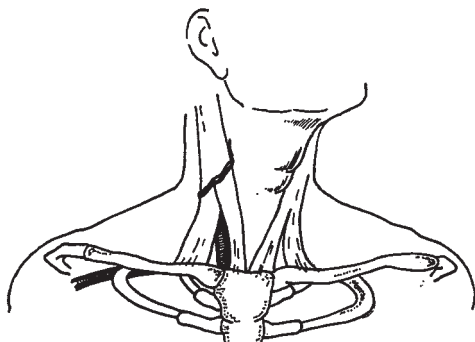


FIGURE 60.1 Neck anatomy.

The needle is inserted under the clavicle at about 1 cm lateral to the sternocleidomastoid muscle insertion point. The needle is then advanced horizontally, nearly parallel to the clavicle, toward the suprasternal notch.

With the supraclavicular approach, the vein is entered from above. The sternocleidomastoid muscle and the clavicle form an angle, and the needle is inserted at this point at a 45° angle. The vein should be cannulated no deeper than 2 cm below the skin surface. If there is uncertainty whether artery or vein has been cannulated, transduce pressure through the needle or obtain a blood gas sample to differentiate vein from artery before dilatation. An instructional video is available from the *New England Journal of Medicine* web site (see reference).

3. The **femoral vein** may also be used for PA catheterization, with the advantages being ease of cannulation, easy compressibility, and absence of pneumothorax risk. Palpate the femoral artery pulse at the level of the inguinal ligament. The femoral vein is usually located 2 cm medial to and 2 cm below the femoral artery. In some patients, the vein may lie closer to the artery. Sometimes, the Valsalva maneuver may make it easier to access the vein.

Unfortunately, there is a high risk of bloodstream infection, associated with central venous access from femoral veins. It is recommended in the Center for Disease Control guidelines for the prevention of intravascular catheter-related infection that it not be used routinely for central venous access.

4. Venous cutdown is rarely necessary, in which case **right basilic and right median cubital veins are used**. However, due to venospasm and difficulty with catheter insertion and advancement, the antecubital route is reserved for those who have failed other routes.

B. PA catheter insertion

1. After the introducer/sheath is placed and secured, the PA catheter can be inserted. Always test balloon inflation, flush the ports, and make sure the catheter is properly calibrated before beginning the procedure. After the PA catheter is tested, insert it through the protective sterile covering and then through the introducer. Keep the balloon deflated at this stage. Ideally, **fluoroscopy and pressure waveforms should be used during PA catheter insertion for guidance**. The catheter should advance easily; if not, do not force the catheter, but make sure the introducer is properly positioned and flushed. Once the catheter has been inserted 15 to 20 cm or after the right atrial (RA) tracing is seen, **inflate the balloon** and advance across the tricuspid valve. The RV tracing should be visualized next, followed by the PA tracing, and finally the pulmonary capillary wedge pressure (PCWP) tracing (see Fig. 60.2). Not infrequently, the RV tracing is accompanied by a few premature ventricular ectopic beats. In general, the PA tracing should be reached within 50 to 55 cm if the catheter is inserted from the IJ vein or subclavian vein or 65 to 70 cm if via a femoral or an arm approach. If the PA tracing has not been visualized by this point, the catheter is likely coiled in the right ventricle. The balloon should be deflated and the catheter withdrawn. The process is repeated until proper placement is achieved.

Once the PCWP tracing is obtained, deflate the balloon and reobtain the wedge pressure by inflating the balloon with 1.5 cm³ of air. If the PCWP tracing is obtained even when the balloon is deflated or with < 1.5 cm³ of air, the catheter has been advanced too far and needs to be pulled back. The pressure waveform should always be closely monitored when inflating balloon-tipped catheters to immediately identify this “overwedging.” The likelihood of PA rupture and infarction increases when catheters are overwedged. In the nonventilated patient, the PCWP should be obtained at end-expiration. In general, wedging the catheter should be avoided in patients with severe PH.

2. It is much easier to float the catheter from the right IJ vein or either subclavian vein. From the femoral veins, it is slightly more difficult, **especially in patients with significant tricuspid regurgitation**. Often, the femoral PA catheter needs

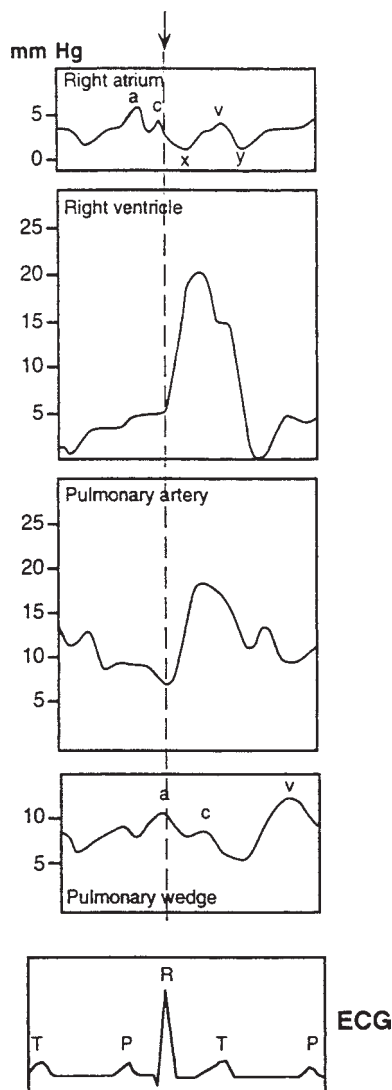


FIGURE 60.2 Waveforms.

to be inserted under fluoroscopic guidance and rotated in a continuous and clockwise motion, with the catheter tip resting just distal to the tricuspid valve until it begins to point upward. Forward motion is then applied to move the catheter into the PA. Alternatively, an S-shaped femoral Swan can be used. When using fluoroscopy, the camera should be in the anteroposterior position, and the balloon should be inflated under fluoroscopy.

3. Finally, check the catheter placement and check for pneumothorax after the procedure by obtaining a chest x-ray film. Catheter placement may be difficult in patients with low CO, severe tricuspid regurgitation, PH, or a dilated right atrium or right ventricle.
4. Catheter advancement may be facilitated by a deep inspiration or, in more difficult cases, by a guidewire with a 0.021" diameter. The wire can be placed inside the distal lumen of the catheter, improving the stiffness and making the catheter easier to manipulate. The distal end of the guidewire should always be under manual control and a hemostat can be placed on the end of the guidewire to ensure this.

V. COMPLICATIONS. See Table 60.2.

VI. TROUBLESHOOTING. See Table 60.3.

VII. WAVEFORMS. See Figure 60.2.

- A. **Right atrium.** When interpreting hemodynamic data, it is helpful to align pressure tracings with simultaneous electrocardiography (ECG). RA systole occurs after the *p* wave on the ECG and produces the *a* wave on the right atrial pressure (RAP) tracing. Atrial relaxation, the *x* descent, occurs with a decline in pressure. Tricuspid valve closure produces a slight upward deflection during the *x* descent, which is known as the *c* wave. The *c* wave follows the *a* wave by the PR interval and correlates with RV systole. The *v* wave occurs near the end of the *t* wave on ECG and marks atrial filling during early diastole. Finally, the *y* descent marks the opening of the tricuspid valve during RV diastole and emptying of the atrium. In the normal right atrium, the peak *a* wave is greater than the peak *v* wave.
- B. **Right ventricle.** RV systole follows the QRS complex of the ECG. With ventricular relaxation, the pressure declines and the tricuspid valve opens. During the continuous filling from the right atrium, a small *a* wave is produced that marks atrial contraction and occurs after the *p* wave and just before the QRS on the ECG. End-diastole is the point just after the *a* wave and just before ventricular contraction. The peak systolic and end-diastolic measurements are used for right ventricular pressures (RVPs).

TABLE 60.3 Troubleshooting in Right Heart Catheterization

Problems	Solutions
Arrhythmia	Catheter may be in the RVOT. Pull the catheter back or advance forward
No PCWP tracing	Catheter tip is usually not advanced far enough, balloon has ruptured, or the catheter is coiled in the right ventricle. Use fluoroscopy for guidance
Continuous PCWP tracing	Balloon is inflated or the catheter is too far advanced ("overwedged")
Abnormal tracing	Catheter tip is up against a vessel wall or is too far advanced
Damped tracing	Tubing is kinked, air or thrombus is in the catheter, or catheter tip is up against the vessel wall. Flush and/or withdraw the catheter
Change in pressure tracing	Improper calibration, change in patient position or catheter location

PCWP, pulmonary capillary wedge pressure; RVOT, right ventricular outflow tract.

- C. Pulmonary artery.** The normal pulmonary arterial pressure (PAP) tracing contains a *v* wave, which corresponds to RV systole and follows the QRS complex. During the relaxation period, pulmonic valve closure produces the incisura, a notch during pressure decline on the *v* wave. The trough of the pressure decline marks end-diastole. Pulmonic arterial systolic pressure, end-diastolic pressure, and mean pressure are recorded.
- D. The PCWP tracing** is a transmitted left atrial pressure (LAP) and is considered an approximation for left ventricular end-diastolic pressure (LVEDP), i.e., LV preload. The waveforms are similar to an RAP tracing, with the *a* wave corresponding to left atrial systole, the *x* descent to relaxation, the *v* wave to filling, and the *y* descent to emptying. However, in contrast to the right atrium, the *v* wave is greater than the *a* wave in the left atrium and the *c* wave is not seen due to transmission through the pulmonary vasculature. Mean PCWP, *a* wave pressure, and *v* wave pressure are generally measured during end-expiration when intrathoracic pressures are equal to the atmospheric pressure.

VIII. PITFALLS OF THE PA CATHETER. While the PA catheter remains the gold standard in monitoring hemodynamics, care should be taken to avoid errors in measurement and interpretation. Clinical decisions based on misleading PA catheter data may adversely impact on patient outcome.

Calibration and referencing. Before the PA catheter enters the body, it should be flushed to eliminate bubbles and calibrated/zeroed at the level of the patient's mid-thorax level, i.e., phlebostatic level. Serial hemodynamic measurements should be performed with the reference point moved to match the phlebostatic level, which changes with patient position.

Proper interpretation of PA catheter data is essential and must be carried out with an understanding of the clinical context. For example, the PCWP is an accurate measurement of LV filling pressure, except in pulmonary veno-occlusive disease (PCWP > LAP) or in mitral stenosis and obstructive left atrial myxoma (PCWP = LAP > LVEDP). In MR, LAP is greater than LVEDP; in acute aortic insufficiency or a noncompliant ventricle, LVEDP is greater than LAP. Furthermore, alterations in pulmonary alveolar and intrathoracic pressures (e.g., in respiratory failure with high positive end-expiratory pressure) can also significantly alter the PAWP waveform.

IX. CARDIAC OUTPUT

- A.** Measurement via **thermodilution** technique may be performed at the bedside but should be avoided in the setting of severe tricuspid regurgitation, intracardiac shunts, existing catheter thrombosis, and low CO.
- (1) Prefill syringes with 10 mL of room temperature indicator (usually normal saline), then connect the syringe to the distal port of the PAC, which should rest in the right atrium.
 - (2) Check the position of the catheter. Make sure you can obtain the PCWP tracing with 1.5 cm³ of air and no less. Then deflate the balloon and ensure the catheter tip rests in the proximal PA.
 - (3) After properly attaching the tubing to the thermistor, inject the contents of the syringe five separate times. Discard the highest and lowest values, taking the mean measurement of the remaining three values.
- B.** Calculation of CO using the **Fick equation**:
- (1) Obtain patient's weight in kilograms.
 - (2) Draw peripheral arterial blood gas to obtain systemic oxygen saturation (A_O₂%).
 - (3) Draw blood gas from the distal lumen of the PA catheter (V_O₂%).
 - (4) Draw hemoglobin.
 - (5) $CO = [Wt \times 3 \text{ mL O}_2/\text{kg}] / [(A_{O_2}\% - V_{O_2}\%) \times 1.36 \times \text{Hgb} \times 10]$.
 - (6) Oxygen consumption can be measured from a metabolic hood or a Douglas bag. It can also be estimated as 3 mL O₂/kg.

TABLE 60.4 Clinical Scenarios in Right Heart Catheterization

Clinical scenarios	Data	Tracing
RV infarct	↑ RAP, ↓ CO, ↓ BP RAP > PCWP, steep γ descent, square root sign (morphology in RV tracing diastolic “dip and plateau”)	Figure 60.3
Acute mitral regurgitation	↑ PCWP, prominent v wave	Figure 60.4
Acute VSD	Oxygen saturation step up from the right atrium to PA	
Noncardiac pulmonary edema	Normal to low PCWP, with abnormal chest X-Ray	
Massive pulmonary embolism	↓ BP, ↓ CO, ↑ PAP, normal PCWP	
Pulmonary arterial hypertension (cor pulmonale)	↑ RAP, ↑ RVP, ↑ PAP, prominent a and v waves and normal PCWP. PAP and RV systolic pressure may reach systemic levels	
Tamponade	Diastolic equalization of pressures (RAP = RV diastolic pressure = PCWP) ↑ RAP, ↑ RVP, ↑ PCWP Paradoxical pulse, blunted γ descent, prominent x descent on RA tracing	Figure 60.5
Constrictive pericarditis	↑ RAP, ↑ PCWP Dip and plateau in RVP tracing, M- or W-shaped jugular venous pressure tracing	Figure 60.6
Tricuspid regurgitation	↑ RAP, ↑ RV EDP Blunted x descent, prominent v wave, steep γ descent, and ventricularization of RAP	

BP, blood pressure; CO, cardiac output; EDP, end-diastolic pressure; PA, pulmonary artery; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; RA, right atrial; RAP, right atrial pressure; RV, right ventricular; RVP, right ventricular pressure; VSD, ventricular septal defect.

X. CLINICAL SCENARIOS. See Table 60.4.

A. Shock (see Table 60.5). Four classes of shock are characterized: hypovolemic, cardiogenic, distributive, and anaphylactic. Hypovolemic shock is due to a profound decrease in venous return and ventricular preload and can be caused by hemorrhage, dehydration, increased positive intrathoracic pressure, and depressed vasomotor tone. Hemodynamic data consist of decreased blood pressure (BP), CO, and PCWP with increased systemic vascular resistance (SVR). Cardiogenic shock results from failure of the cardiac pump to maintain adequate output and can be caused by a change in loading conditions (decrease in preload due to tamponade or increase in preload due to VSD), contractility (acute ischemia or infarction), or an abrupt increase in afterload. Low BP and CO but high PCWP and SVR characterize cardiogenic shock due to LV dysfunction. Contrary to classic teaching, patients in cardiogenic shock from predominant LV failure can have normal to reduced SVR. This drop in SVR in the setting of an MI is most commonly seen after a large anterior wall MI and among the elderly and is likely mediated by profound nitric oxide release in the setting of acute myocardial injury. In general, predominant elevation of RAP is indicative of RV failure, and isolated elevation of the PCWP is indicative of LV failure. The

TABLE 60.5 Interpreting Right Heart Catheterization Data in Shock

	Blood pressure	PCWP	CO	SVR
Distributive	Low	Low	High	Low
Cardiogenic	Low	High	Low	High/normal/low
Hypovolemic	Low	Low	Low	High

CO, cardiac output; PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

hemodynamic indices characteristic of distributive shock are low BP, PCWP and SVR but high CO. A depressed CO as well as low BP, PCWP, and SVR can characterize the late phase of distributive shock. Finally, in terms of hemodynamics, not much is known about anaphylactic shock. However, there is a hyperkinetic phase, characterized by low SVR and high CO, as well as a later hypokinetic phase, dominated by profound hypovolemia with decreased CO.

- B. RV failure** (see Fig. 60.3 and Table 60.4) may be due to RV infarction, severe PH, pulmonary embolism, or increased preload due to left-to-right intracardiac shunt. An RV infarct (see Fig. 60.3) produces increased RAP and RV end-diastolic pressure, with low CO and BP. Because the right ventricle dilates and becomes less distensible, a dip-and-plateau pattern on the RVP tracing is seen. On the RAP tracing, there is a steep *y* descent. In the setting of severe tricuspid regurgitation and RV infarction, the dip-and-plateau pattern is lost. A blunted *x* descent, prominent *v* wave, and steep *y* descent are then seen on RAP tracing.
- C. Acute MR** (see Fig. 60.4 and Table 60.4) may be due to papillary muscle dysfunction or rupture. In this setting, the left atrium is subjected to a sudden increase in pressure. Regurgitation produces a large *v* wave in the PCWP tracing that occurs after the *T* wave on ECG. A *v*-wave pressure that is twice the value of PCWP is considered to be abnormal. In chronic MR, the *v* wave may be modest in amplitude due to chronic atrial dilatation. Other causes for prominent *v* waves are severe tricuspid regurgitation and VSD.
- D. Tricuspid regurgitation** (see Table 60.4). The RA systolic wave may resemble the RV tracing. There is increased RAP and RV end-diastolic pressure, a blunted *x* descent, a prominent “*c-v*” wave, and a steep *y* descent on RAP tracing.

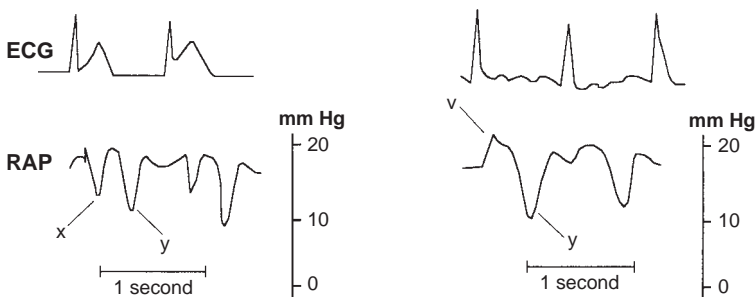


FIGURE 60.3 Right ventricular infarction without tricuspid regurgitation (*left*); right ventricular infarction with tricuspid regurgitation (*right*).

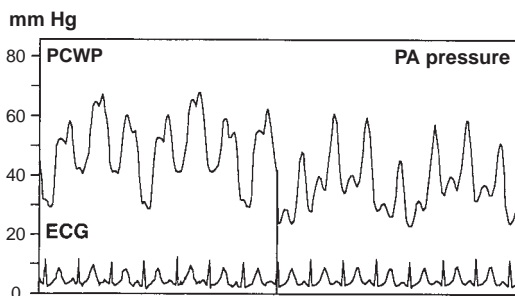


FIGURE 60.4 Acute mitral regurgitation.

- E. Cardiac tamponade** (see Fig. 60.5 and Table 60.4). The hallmark of tamponade is diastolic equalization of pressures, where $RAP = RVP = PCWP$. The RA waveform is characterized by a deep x descent and absent y descent (due to lack of RV filling at the beginning of diastole). In addition, RAP, RVP, and PCWP are increased.
- F. Constrictive pericarditis** (see Fig. 60.6 and Table 60.4) is characterized by brisk ventricular filling during early diastole and limited ventricular filling during late diastole. The constriction results in the elevation and equalization of RV end-diastolic pressure and LVEDP. The dip-and-plateau waveform is seen in constrictive pericarditis as well as restrictive cardiomyopathy, RV infarct, and massive pulmonary embolism.
- G. Massive pulmonary embolism** (see Table 60.4). There is ventricularization of the PA waveform with rapid end-systolic descent and a hardly visible, or absent, diastolic notch due to obstruction in the PA.
- H. Restrictive cardiomyopathy** (see Table 60.6) includes a heterogeneous group of illnesses, such as hemochromatosis, amyloidosis, and endomyocardial fibrosis. This leads to impaired diastolic filling of the ventricles. There is a prominent y descent, but the dip-and-plateau waveform is less pronounced due to a pandiastolic hindrance to ventricular filling.
- I. Pulmonary hypertension** (see Table 60.4). PH is defined as a mean PAP > 25 mm Hg at rest. It can be caused by elevated pulmonary venous pressures due to LV dysfunction, left-sided valvular disease, and/or volume overload (i.e., elevated PCWP). It may also be caused by intrinsic pathology within the pulmonary arterial bed, i.e., pulmonary arterial hypertension (PAH). PAH is defined as mean PAP > 25 mm Hg at rest with PCWP < 15 mm Hg. Compensatory changes in the right heart to chronic PH or PAH result in elevations in RV and PA pressures with prominent a and v waves.

XI. FORMULAS (see Table 60.7)

- (1) **CO** by Fick equation in L/min:

$$CO = [Wt \times 3 \text{ mL O}_2/\text{kg}] / [(A_{O_2}\% - V_{O_2}\%) \times 1.36 \times \text{Hgb} \times 10]$$

where Wt is weight in kilograms, $A_{O_2}\%$ is systemic arterial oxygen saturation, $V_{O_2}\%$ is mixed venous oxygen saturation, and Hgb is hemoglobin concentration.

- (2) **Cardiac index (CI)** in L/min/m²:

$$CI = CO/BSA$$

where BSA is body surface area in m².

- (3) **Stroke volume (SV)** in mL/beat:

$$SV = CO/\text{heart rate}$$

- (4) **Pulmonary vascular resistance (PVR)** in dynes \times s/cm⁵:

$$PVR = [(\text{mean PAP} - \text{PCWP}) \times 80] / [CO]$$

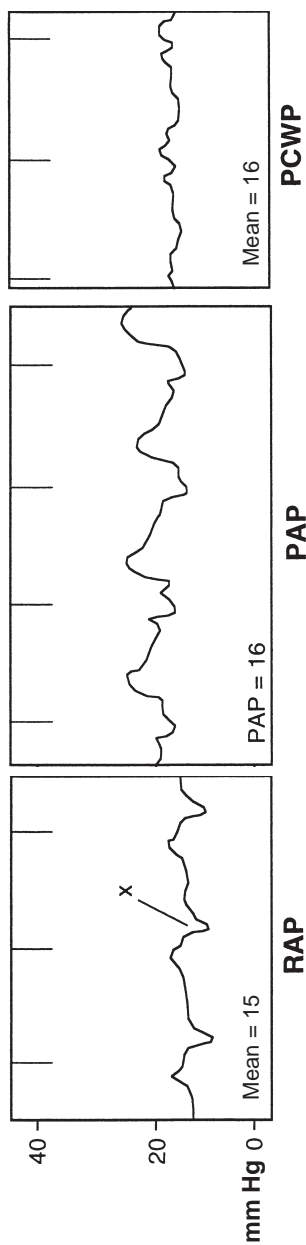


FIGURE 60.5 Cardiac tamponade.

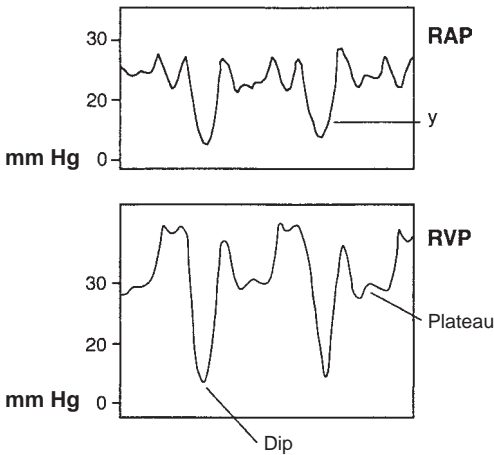


FIGURE 60.6 Constrictive pericarditis.

TABLE 60.6 Differentiating Diastolic Dysfunction

	Constrictive pericarditis	RV infarct	Tamponade	Restrictive cardiomyopathy
Pulsus paradoxus	Rare	Occasional	Frequent	Rare
RA waveforms	Prominent y descent	Prominent y descent	Prominent x descent	Prominent y descent
Equalization of diastolic pressures	Frequent	Frequent	Frequent	Rare
Dip and plateau (RV)	Frequent	Frequent	Absent	Frequent

RA, right atrial; RV, right ventricular.

where PAP is pulmonary arterial pressure and PCWP is pulmonary capillary wedge pressure.

- (5) **Systemic vascular resistance** in dynes \times cm⁵:

$$SVR = [(MAP - CVP) \times 80] / [CO]$$

where MAP is mean arterial pressure and CVP is central venous pressure (can also substitute RAP for CVP).

- (6) **Estimate of O₂ consumption** = 125 mL/min/m² = 3 mL O₂/kg.
 (7) **O₂ content** = (A_{O₂}% - V_{O₂}%) \times 1.36 \times Hgb \times 10.
 (8) **CO** = O₂ consumption / O₂ content.

XII. INTRACARDIAC SHUNT. The existence of an intracardiac shunt can be evaluated by using a PA catheter and performing a saturation “run.” Blood samples for oximetry are obtained from the PA as well as regions of the right ventricle, right atrium, superior vena cava, and inferior vena cava. With the catheter positioned in the PA, CO by the Fick equation can be obtained. As the operator manipulates and pulls the catheter back under fluoroscopic and pressure guidance, a blood sample from each location is

TABLE 60.7 Normal Values and Formulas

	Formula	Normal values
RA		0–8 mm Hg
RV		Systolic 15–30 mm Hg Diastolic 0–8 mm Hg
PA		Systolic 15–30 mm Hg Diastolic 3–12 mm Hg Mean 8–20 mm Hg
PCWP		6–12 mm Hg
CO	Fick equation: $[Wt \times 3 \text{ mL/kg}] / [(A_{O_2}\% - V_{O_2}\% \times 1.36 \times \text{Hgb} \times 10)]$	4–8 L/min
CI	CO/BSA	2.8–4.2 L/min/m ²
SV	CO/HR	40–120 cm ³ /beat
SVR	$[(MAP - CVP) \times 80] / CO$	770–1,500 dynes s/cm ²
PVR	$[(PAP - PCWP) \times 80] / CO$	20–120 dynes s/cm ²
Shunt fraction (Q_p/Q_s)	$[A_{O_2}\% - V_{O_2}\%] / [PV_{O_2}\% - PA_{O_2}\%]$	> 2.0 large defect 1.5–2.0 moderate defect

$A_{O_2}\%$, peripheral arterial oxygen saturation; BSA, body surface area; CI, cardiac index; CO, cardiac output; CVP, central venous pressure; Hgb, hemoglobin; HR, heart rate; MAP, mean arterial pressure; PA, pulmonary artery; $PA_{O_2}\%$, pulmonary artery oxygen saturation; PAP, pulmonary arterial pressure; PCWP, pulmonary capillary wedge pressure; $PV_{O_2}\%$, pulmonary vein oxygen saturation often assumed to equal $A_{O_2}\%$ in left-to-right shunt; PVR, pulmonary vascular resistance; Q_p , pulmonary flow; Q_s , systemic flow; RA, right atrium; RV, right ventricle; SV, stroke volume; SVR, systemic vascular resistance; $V_{O_2}\%$, mixed venous oxygen saturation, Wt, weight in kilograms.

aspirated. A left-to-right shunt is suggested when a “step up,” or increase, in the oxygen saturation in one chamber exceeds the oxygen saturation of a proximal compartment by more than 7% in the case of an atrial shunt or more than 5% in ventricular or great vessel shunts.

In a normal setting, the effective pulmonary blood flow should equal the systemic blood flow ie. $Q_p/Q_s = 1$. However, with a left-to-right shunt, pulmonary blood flow is equal to systemic blood flow plus the amount of shunt flow. Conversely, in a right-to-left shunt, the effective pulmonary blood flow is decreased by the amount of shunt flow. The shunt fraction is the ratio of pulmonary to systemic flow, denoted Q_p/Q_s (where Q_p is pulmonary flow and Q_s is systemic flow). For an atrial septal defect, the mixed venous oxygen saturation is computed as the sum of three times the superior vena cava saturation plus the inferior vena cava oxygen saturation, and the total is divided by 4.

A. Calculation of left-to-right shunt

(1) **Shunt fraction = pulmonary flow in L/min (Q_p)/systemic flow in L/min (Q_s)**

(2) **$Q_p = O_2$ consumption/[10 × ($PV_{O_2}\% - PA_{O_2}\%$)]**

where $PV_{O_2}\%$ is pulmonary vein oxygen saturation and $PA_{O_2}\%$ is pulmonary artery oxygen saturation.

(3) **$Q_s = O_2$ consumption/[10 × ($A_{O_2}\% - MV_{O_2}\%$)]**

where $A_{O_2}\%$ is peripheral arterial oxygen saturation and $MV_{O_2}\%$ is mixed venous oxygen saturation.

(4) **Simplified calculation** using saturation only:

$$Q_p/Q_s = (A_{O_2}\% - MV_{O_2}\%)/(PV_{O_2}\% - PA_{O_2}\%)$$

Important note: A shunt fraction of > 1.5 often necessitates shunt closure.

ACKNOWLEDGMENTS: *The authors wish to acknowledge the contributions of Dr. Kellan E. Ashley and Dr. Leslie Cho to previous editions of this chapter.*

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Endomyocardial Biopsy

I. INDICATIONS AND CONTRAINDICATIONS. Endomyocardial biopsy (EMB) is less used now as a diagnostic tool for patients with systolic or diastolic dysfunction with the availability of more accurate noninvasive imaging techniques such as magnetic resonance imaging. Currently, the major indications for EMB are monitoring for allograft rejection after cardiac transplantation, as well as ruling out some potentially treatable forms of myocarditis. The role for this procedure in other disorders, such as arrhythmogenic right ventricular dysplasia, remains controversial because the diagnostic accuracy must be considered in relation to the lack of proven effective therapy. Potential indications and contraindications for EMB are listed in Tables 61.1, 61.2, and 61.3.

II. PATIENT PREPARATION. As with any other procedure, extensive patient education and informed consent are necessary before starting the procedure. Patients undergoing EMB should be informed that there is a very small chance (<1% in experienced hands) of cardiac perforation, with potential urgent cardiovascular surgery and even death as a consequence.

Sedation is seldom needed but may help anxious patients better tolerate the procedure. Monitoring of heart rate by continuous electrocardiographic telemetry, blood pressure (noninvasively), and pulse oximetry is essential throughout the procedure. The patient should be monitored for a couple of hours after the procedure, as myocardial perforation with subsequent pericardial effusion may only become apparent some time after EMB. The patient is always positioned flat regardless of the venous approach. Venous access may be obtained through the internal jugular (most common), subclavian, or femoral veins. Ultrasound guidance or maneuvers to increase central venous pressure such as Valsalva, leg elevation with a wedge, and Trendelenburg position are helpful in obtaining venous access. Most centers use fluoroscopy as the imaging method of choice to guide EMB. However, echocardiography can also be used, particularly when radiation exposure needs to be minimized, such as in pregnant women.

III. DEVICES

A. Sheath. Venous access is obtained using the Seldinger technique, and the sheath is always placed over a guidewire so as not to damage any vascular structures. A standard short sheath (11 cm, 7F or 8F) is generally sufficient for the right internal jugular or any subclavian approach. The intermediate-length sheath (24 or 35 cm) may be helpful to reduce venous angulation or to avoid damaging the vessel wall or a suture line when inserting the biptome in patients with prior heart transplantation. For the left internal jugular approach, a longer sheath (40 cm, 7F) is used with a single- or double-curved tip based on operator preference and venous and cardiac anatomy. For a femoral approach, a curved 7F, 85-cm-long transeptal sheath is used, as it can be easily positioned into the right ventricle.

TABLE 61.1 Common Indications for Endomyocardial Biopsy

Clinical scenarios	Class of recommendation
New-onset heart failure of <2 wk duration associated with a normal-sized or dilated left ventricle and hemodynamic compromise	I
New-onset heart failure of 2 wk to 3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	I
Heart failure of >3 mo duration associated with a dilated left ventricle and new ventricular arrhythmias, second- or third-degree heart block, or failure to respond to usual care within 1–2 wk	IIa
Heart failure associated with a DCM of any duration associated with suspected allergic reaction and/or eosinophilia	IIa
Heart failure associated with suspected anthracycline cardiomyopathy	IIa
Heart failure associated with unexplained restrictive cardiomyopathy	IIa
Suspected cardiac tumors	IIa
Unexplained cardiomyopathy in children	IIa

DCM, dilated cardiomyopathy.

Adapted from AHA/ACC/ESC 2007 Consensus Statement.

TABLE 61.2 Conditions Involving the Heart in Which Endomyocardial Biopsy Can Establish the Diagnosis, Listed According to the Presence or Absence of Proven Effective Therapy

Treatable conditions	Less treatable conditions
Cardiac allograft rejection	Myocarditis (non-giant cell)
Cardiac amyloidosis	Arrhythmogenic right ventricular dysplasia
Giant cell myocarditis	Glycogen storage disease
Hypereosinophilic syndrome	Rheumatic carditis
Staging of anthracycline toxicity	Chagas disease
Cardiac sarcoidosis	
Cardiac hemochromatosis	
Lyme carditis	
Fabry's disease	

B. Bioptome. There are two basic types of bioptomes: (1) independent and stiff, which does not require a long sheath but does rely on the operator skill to be maneuvered safely into the right ventricle, and (2) flexible, which requires a longer sheath advanced into the right ventricle for positioning. Resterilizable and reusable bioptomes are widely used, but disposable bioptomes are also available. For internal jugular and subclavian approaches, 50-cm-long bioptomes are used, whereas for femoral access, the bioptomes used are longer (up to 105 cm).

TABLE 61.3 Relative Contraindications for Endomyocardial Biopsy

Informed consent not obtained
Patient not cooperative (confused, agitated, etc.)
Profound hemodynamic compromise
No cardiac surgery backup available
Coagulopathy (INR > 1.5)
Mechanical tricuspid prosthesis
Significant right-to-left shunt (risk of air embolus)
Thinning of myocardium after MI or in case of ARVD
RA or RV thrombus

ARVD, arrhythmogenic right ventricular dysplasia; INR, international normalized ratio; MI, myocardial infarction; RA, right atrial; RV, right ventricular.

IV. TECHNIQUE. Right ventricular endomyocardial biopsies can be performed from either the right or left internal jugular, subclavian, or femoral veins. If necessary, a left ventricular EMB can be obtained via the femoral artery approach, although this is rarely necessary.

A. Right ventricular biopsy

1. Internal jugular vein approach. After standard preparation and local anesthesia, the required anatomic landmarks (see Chapter 58) are identified. A pilot puncture with a 22G needle can be made to localize the vein. The internal jugular vein is punctured with an 18G (Cook) needle, and the sheath is introduced using standard technique. The biptome, with jaws closed and tip straightened, is advanced under fluoroscopic or echocardiographic guidance across the atrial suture line (in allografts) until its tip lies against the lower third of the lateral right atrial wall. It is then rotated gently counterclockwise and simultaneously advanced into the right ventricular cavity. During this procedure, the tip is gently unstraightened. Rotation is continued until the catheter reaches the apical half of the right ventricle and the handle clamp points in the posterior direction. At this point, the tip of the biptome rests on the interventricular septum. The position is confirmed by inability to further advance the biptome, the generation of premature ventricular contractions, and fluoroscopic appearance. Generation of premature atrial contractions or absence of ventricular ectopy may indicate that the biptome was advanced in the right atrium or in the coronary sinus. If there is any doubt about the position, the biptome is withdrawn and the process repeated. Once in the desired position, the biptome is withdrawn about 0.5 to 1 cm and advanced again after the jaws have been opened. When it touches the endocardium, the jaws are closed and the biptome is gently withdrawn with its jaws closed under continuous fluoroscopic guidance. A small tug is often felt while withdrawing, but excessive tugging and multiple premature ventricular contractions should prompt consideration of repositioning. Usually four to six biopsy specimens are obtained in different areas of the septum to reduce sampling error. Once the procedure is completed, the venous sheath is removed and hemostasis achieved. Patients are monitored for about 2 to 4 hours after EMB.

2. Femoral vein approach. After standard preparation and local anesthesia, the required anatomic landmarks (see Chapter 60) are identified. The right (more common) or the left femoral vein is punctured with an 18G (Cook) needle, and a 0.038" guidewire is advanced up to the right atrium. A long (85-cm) 7F sheath

with dilator is advanced over the wire, and on entering the right atrium the dilator is withdrawn. The tricuspid valve is crossed with the help of the guidewire (a balloon-tipped catheter can also be used), and the sheath is advanced into the right ventricle toward the intraventricular septum. The pressure tracing, occurrence of ventricular ectopy, and fluoroscopy are used to confirm position. The side port of the sheath may be connected to a slow continuous intravenous infusion to prevent clot formation inside the sheath, especially if a long procedure is anticipated. A long nonsteerable biptome is advanced through the sheath and is used to acquire samples. Biopsies are taken in a manner similar to that of the internal jugular vein approach.

3. **Subclavian vein approach.** After standard preparation and local anesthesia, the required anatomic landmarks (see Chapter 60) are identified. The subclavian vein is punctured using an 18G (Cook) needle followed by insertion of the sheath. The occurrence of ventricular ectopy and fluoroscopic images are used to confirm a position pointing toward the interventricular septum. Biopsies are taken as with the internal jugular vein approach.

B. Left ventricular biopsy

1. **Femoral arterial approach.** After standard preparation and local anesthesia, the required anatomic landmarks are identified. The right (more common) or left femoral artery is punctured with an 18G (Cook) needle, and a short 8F sheath is inserted while a 0.035" long exchange guidewire is advanced up to the ascending aorta. A regular-length 7F pigtail catheter is advanced over the wire, and the aortic valve is crossed in the conventional manner. Afterward, the pigtail catheter is removed, while leaving the guidewire in the left ventricle, and exchanged with an 8F long, curved guiding sheath. The tip of this sheath is directed toward the interventricular septum, distal to the mitral apparatus, away from the thinner posterobasal wall. The position of the sheath is carefully reconfirmed (fluoroscopic images in two angulations and pressure tracings), and 5,000 U heparin is given intravenously before insertion of the biptome. A long, nonsteerable biptome is then advanced through the guiding sheath, and biopsy samples are collected as with right ventricular biopsy. It is important to note that catheters must be aspirated and flushed after each biopsy, since air can enter the sheath and clots can form in the sheath after removing the biptome. Heparin is not reversed with protamine at the end of the procedure as it is thought to minimize thrombus formation at the biopsy sites.

V. COMPLICATIONS. In general, EMB can be performed more safely in heart transplant recipients than in patients with native hearts, because of the scarred and thickened pericardium in transplanted patients.

- A. **Mortality.** Procedure-related deaths have been reported to be <0.05% in contemporary series.
- B. **Cardiac perforation and tamponade.** The reported incidence of cardiac perforation is 0.3% to 0.5%, which can rapidly result in tamponade. The risk can be minimized by careful monitoring of catheter position to ensure that biopsies are obtained from the thicker interventricular septum and by gentle catheter advancement and EMB procurement. Symptoms of chest pain during or after the procedure, shortness of breath, a pericardial rub, or altered hemodynamics should suggest potential perforation and should prompt urgent echocardiography to rule out a new pericardial effusion or tamponade. Patients in whom a new pericardial effusion is suspected or detected should be monitored in the hospital for evidence of increasing pericardial effusion or tamponade, and an echocardiogram should be repeated at intervals as necessary and before discharge.

In patients early after heart transplantation, the atrial suture line also poses a higher risk of perforation. Very gentle advancement of the biptome (and pulling back if any resistance is felt) and use of a longer sheath to pass the suture line if

needed will reduce this risk. Patients with suspected perforation should be closely monitored, and echocardiography, fluoroscopy, and cardiac tomography scanning can be used to confirm the diagnosis.

For both cardiac perforation and tamponade, careful monitoring is usually sufficient, although pericardiocentesis or even urgent cardiac surgery may be necessary if hemodynamic compromise develops.

- C. **Thromboembolism.** Right-sided thromboembolism during EMB is possible in theory, but does not cause any clinically significant sequelae if it occurs. The risk of arterial embolization during left ventricular EMB is higher, owing to the longer sheath, and may have catastrophic consequences. Using heparin during a left-sided approach and aspirating air and flushing the sheath before inserting the bioptome minimize the risk of embolism.
- D. **Arrhythmia.** Occasionally, a sustained atrial or, less commonly, a ventricular tachycardia is induced by EMB. These arrhythmias are almost always stopped by touching the wall of the right atrium or ventricle with the bioptome. Bradyarrhythmic episodes or bundle branch block induced by EMB is very rare and responds only to β_1 -stimulants and not to atropine in heart transplant patients.
- E. **Tricuspid valve (or mitral valve for left ventricular biopsy) dysfunction.** The bioptome can damage the chordae or papillary muscle and produce significant valvular regurgitation. The risk of this complication is minimized by careful confirmation of bioptome position before sampling. The cumulative risk of this complication is greater in heart transplant patients because they undergo many EMB procedures.
- F. **Damage to vena cava, coronary sinus, hepatic vein, and coronary arteries.** Gentle advancement of the bioptome, use of a longer sheath, retraction of bioptome whenever resistance is felt, and position confirmation with multiple fluoroscopic views may minimize these complications. Fistula formation from a coronary artery branch to the right ventricle has occurred following EMB but is of no clinical significance.
- G. **Local complications.** Hematoma, local infection, and injury to the lung (pneumothorax, incidence 0.9%) and nerve (recurrent laryngeal palsy and Horner's syndrome) are possible but rare while achieving vascular access. Careful identification of anatomic landmarks reduces the risk of these complications.
- H. **Pain.** The EMB itself is usually painless, but some patients experience some mild degree of pain when the bioptome touches the heart or when a biopsy is taken.

ACKNOWLEDGMENTS: *The authors would like to thank Drs. Milind Shah, Wilfried Mullens, and Zubeir Adams for their contributions to earlier editions of this chapter.*

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Management of Continuous-Flow Ventricular Assist Systems: Troubleshooting and Complications

- I. INTRODUCTION.** This chapter is designed to briefly overview the mechanics of continuous-flow left ventricular assist systems (LVASs) and highlight the diagnosis and management of immediate and long-term complications of LVASs. LVAS support has emerged as the standard of care in patients with refractory stage D heart failure (HF) as both bridge to transplant and destination therapy.
- (A) Continuous-flow LVASs are the most recent advances in permanent mechanical support systems.
 - (B) Continuous-flow LVAS can use either centrifugal-flow or axial-flow blood pumps. Both are designed similarly with a single rotating impeller that is designed to increase pressure and flow within the system.
 - (C) Bearings constrain the impeller within the device, allowing rotational movement. The bearings may be of three types: magnetic levitation, hydrodynamic, and blood immersed.
 - (D) Continuous-flow LVASs are smaller than pulsatile ventricular assist devices (VADs) that can accommodate most patients, including small women and children.
 - (E) Blood flow capacity is up to 10 L/min, which can provide constant unloading of the left ventricle. Unlike pulsatile-flow pumps that are primarily preload dependent, continuous-flow VADs are both afterload and preload dependent.
 - (F) As pulsatile VADs had either an automatic or fixed rate and stroke volume, continuous-flow VADs can be modulated by changes in the rotational velocity of the impeller.
 - (G) Axial-flow pumps include Thoratec Heartmate II, Jarvik 2000, HeartAssist 5, Incor, and Synergy.
 - (H) Centrifugal pumps include HeartWare HVAD, DuraHeart, Levacor VAD, and EVAHEART LVAS.
 - (I) HeartMate II is the most studied LVAS and has recently gained FDA approval for bridge to transplant and destination therapy. Jarvik 2000, HeartAssist 5, HeartWare HVAD, DuraHeart, Levacor VAD, and EVAHEART LVAS currently have investigational trial exemption for bridge to transplant in the United States.
 - (J) The use of implantable devices for lifetime support (destination therapy) has increased significantly since approval of the HeartMate II in 2010. As the technology improves, complications decrease, and more candidates for permanent mechanical support are identified, we will see more patients with permanent VADs in almost all cardiology clinical settings.
- II. PREOPERATIVE CONSIDERATIONS.** Patient selection, preimplant considerations, and implant timing are critical in optimizing outcomes in patients receiving LVAS support.

- A. Patient selection** involves determining the appropriateness for mechanical circulatory support, operative mortality, and family/social support at discharge.
- (1) Highest risk of mortality is prior to discharge from hospital.
 - (2) Trend at many large centers is to implant early to minimize or avoid progressive end-organ damage.
 - (3) Important preimplant medical factors include nutritional status, pulmonary vascular resistance, improve congestive hepatopathy and nephropathy, and optimize right heart function, candidacy for coagulation, underlying infections, and other end-organ dysfunction (renal, hepatic, and pulmonary).
 - (4) Other important preimplant factors include patient's social support system, psychosocial status, and the ability to care for the device itself.
- B. Interagency Registry of Mechanically Assisted Circulatory Support (INTERMACS) patient profiles.** INTERMACS is a registry designed to track patient selection, outcomes, and adverse events. Since inception, it has enrolled close to 6,000 patients and has provided key observations to improve patient selection and outcomes.
- (1) INTERMACS (see Table 62.1) has defined patient profiles that highlight risk and timing of implantation.

TABLE 62.1 Interagency Registry of Mechanically Assisted Circulatory Support Patient Profile

Profile	Description	Comment
1	Critical cardiogenic shock	"Crash and burn profile." Definitive therapy is needed within hours. Has the lowest survival
2	Progressive decline on inotropic support	Inotropic-dependent patients. Progressive decline such as worsening renal function, nutritional status, or volume status despite increased inotropic support. Definitive therapy is needed within days
3	Stable but not inotrope dependent	Stable on lower doses of inotropes, but unable to wean. Stable volume status, organ function, and nutrition, but inotropic dependent. Elective therapy may be needed within weeks to a few months. Profile 3 has the best outcomes
4	Resting symptoms home on oral therapy	Patients have daily symptoms requiring fluctuating high-level doses of diuretics. Elective therapy may be needed within weeks to a few months. Outcomes for this level are under investigation for appropriateness
5	Exertion intolerant	Evidence of refractory volume-overloaded state. Able to perform ADLs and comfortable at rest, but have refractory symptoms with exertion or in a persistently volume-overloaded state. Patients in INTERMACS level 4 may overlap with this profile. Outcomes for this level are under investigation for appropriateness
6	Exertion limited	No evidence of refractory volume-overloaded state. Able to perform ADLs and comfortable at rest. Limited by symptoms within minutes of meaningful activity. Outcomes for this level are under investigation for appropriateness
7	Advanced NYHA class III symptoms	Transplantation or mechanical circulatory support is not currently indicated in this profile

ADLs, activities of daily living; INTERMACS, Interagency Registry of Mechanically Assisted Circulatory Support; NYHA, New York Heart Association.

III. TERMS AND BASIC MECHANICS OF LVASs. Basic terms, mechanics, and physiology are outlined in this section. When evaluating a patient with LVAS, no single parameter should be used for diagnosis.

- A. Basic mechanism.** Volume of flow is determined by the speed of the rotary impeller and the change of pressure across the pump. At a fixed speed, flow is inversely related to pressure. Thus, when the pump pressure increases, the flow will decrease at a fixed speed.
- B. Pump differential pressure** is equal to the aortic pressure minus the left ventricular (LV) pressure. Since the aortic pressure typically remains unchanged within a normal range, the change in pump differential pressure is primarily dependent on the LV pressure.
- C. Pump speed** is a direct measurement of the rotational velocity. Continuous-flow ventricular assist system operates at a fixed pump speed. The optimal pump speed is typically determined by a ramp study (see Section IV). Substantial changes in pump speed are usually associated with abnormal conditions. Abrupt drops in pump speed followed by normalization may indicate suction events (see below).
- D. Pump power** is a direct measure of motor voltage and current (power = current voltage difference). Pump speed, flow, and demand directly affect power. Gradual or sudden sustained increases in power may signify thrombus or debris accumulation in the motor.
- E. Pump flow** is a calculated measurement that essentially maintains a linear relationship with power at a given speed. Within normal ranges, increased power results in increased flow. However, inherent to being a calculated value, pump flows may become unreliable at the low and high extremes of the flow–power relationship. For example, a thrombus may cause an abrupt increase in power and an incorrect calculation of increased flow. Suction events may also lead to incorrect flow values. Thus, in a given clinical situation, further assessment of pump function is required.
- F. Pulsatility index (PI)** is the averaged measure of the magnitude of flow pulses over a 15-second interval. Flow pulses are determined by the contractile function of the left ventricle that produces changes in ventricular pressure. Higher PI values (range 1 to 10+) indicate greater LV contribution (filling and contractility), whereas lower PI values represent greater mechanical pump contribution. While the patient is at rest, there should be little change in the PI. Decreased PI may represent underfilling due to a change in contractile function or hypovolemia.
- G. Suction event** occurs when the LV pressure becomes so negative that the left ventricle collapses.

IV. RAMPED SPEED STUDY. This is a method used to determine the speed that is the safest for the patient and provides the optimal LVAS support. Optimal speed is achieved when cardiac index, septum position, and LV dimensions are within normal ranges.

- A. Initial optimum speed** is determined ideally while still in the operating room with transesophageal echocardiography.
- B.** Ramped speed studies are best performed on hemodynamically stable, euvoletic patients and may use transthoracic echocardiography.
- C.** Evaluation can be performed with echocardiography or invasive hemodynamics.
- D.** Determination of **low fixed speed** is achieved by gradually decreasing the pump speed until the patient becomes symptomatic and the aortic valve opens with every beat when cardiac index falls below 2.5 L/min/m^2 or pulmonary vascular resistance begins to increase. For the HeartMate II, speed should never go below 8,000 rpm. At the low fixed speed, record the LV diameter, septal position, patient vitals, and, if available, hemodynamics.
- E.** Determination of **high fixed speed** is achieved by increasing the rotational velocity of the pump until there is intraventricular flattening by echocardiography

(parasternal long or four-chamber view). At the high fixed speed, record the LV diameter, frequency of the aortic valve opening, patient vitals, and, if available, hemodynamics.

- F. Determination of the **optimum fixed speed** is typically the median of the low fixed speed and high fixed speed. However, this speed should be adjusted based on clinical judgment as well as the desired frequency of aortic valve openings. It is also recommended that the pump speed is at least 400 rpm below the high fixed speed.

V. PUMP PARAMETER ABNORMALITIES

A. Pump speed

- (1) Large speed changes in fixed speed mode are abnormal.
- (2) A suction event has two phases of pump speed change: initial decrease to lower limit at the beginning of the suction event followed by a gradual increase to fixed speed at the end of the suction event.
- (3) In the absence of suction events, consider primary pump or control issues.

B. Pump power

- (1) Normal changes in power may be due to increased flow and demand or change in speed.
- (2) Abrupt increases in power may be associated with pump thrombus.
- (3) Gradual increases in power may be associated with in situ formation of bearing thrombus or bearing deposition.

C. Pump flow

- (1) Flow is the calculated value based on pump speed and power. It becomes an imprecise estimation at extremely high and low values.
- (2) Changes in flows should be used in parallel with other device and clinical parameters.
- (3) During pump or bearing thrombus events, pump flow will be abnormally elevated.

D. Pulsatility index

- (1) Under normal conditions, PI can increase with increased preload and LV contractility.
- (2) Decreases in PI typically warrant further investigation as this may represent hypovolemia, obstruction of the inflow or outflow tract, or thrombus.

VI. DEVICE COMPLICATIONS

A. Suction event

- 1. Signs: Arrhythmias (ventricular tachycardia) and hypotension.
- 2. Parameter changes: In the HeartMate II, speed automatically decreases to low fixed speed followed by slow increase to set speed. Pump flow decreases.
- 3. Management: Chest radiograph to assess inflow cannula position. Assess volume status to rule out hypovolemia and assess right ventricular (RV) function. Consider decreasing pump speed with ramped speed study.

B. Inflow tract obstruction

- 1. Signs: New-onset HF symptoms, arrhythmias, and hemolysis.
- 2. Parameter changes: Increased pump power, decreased pump flow, and PI. High velocities across inflow by Doppler echocardiography.
- 3. Management: Consider reducing speed if septal obstruction is noted on ramped speed study. Chest radiography to assess inlet position (supine and upright). Echocardiography for tamponade and right heart function. Computed tomography scan to assess inflow cannula position.

C. Outflow tract obstruction

- 1. Signs: New-onset HF symptoms and hemolysis.
- 2. Parameter changes: Increased pump power, decreased pump flow, and PI.

3. Management: Ramped speed study looking for changes in LV dimension and in diastolic arterial pressures with speed changes. Echocardiography and angiography for outlet position and the presence of graft kink.

D. Deposition of thrombus

1. Signs: New-onset HF symptoms, hemolysis, change in pump sound with auscultation, and hypotension with increased pulse pressure.
2. Parameter changes: Increased pump power, pump flow, and decreased PI.
3. Management: Angiography and echocardiography to assess pump flow. Heparin may slow progression of thrombus formation. Consider thrombolytics (rarely). Consider pump replacement.

E. Mechanical pump failure

1. Signs: New-onset HF symptoms, vibration of pump, and hypotension with increased pulse pressure.
2. Parameter changes: Cannot maintain pump speed, PI > 10, and multiple red heart alarms.
3. Management: Contact surgeon. Consider replacement of pump.

VII. SPECIFIC CLINICAL SCENARIOS FOR PATIENTS WITH LEFT VENTRICULAR ASSIST DEVICE (LVAD)

Diagnosis and management of clinical changes in patients with LVAD should include, when appropriate, physical examination and multimodality imaging: echocardiography, computed tomography, radiography, and invasive hemodynamics.

A. Hypovolemia

1. Signs: Hypotension and possible suction events causing syncope or arrhythmias.
2. Echocardiography may demonstrate decreased RV and LV dimensions.
3. Parameter changes encountered: Decreased PI.
4. Suggested management: Consider adjustment of diuretics, decreasing pump speed, and volume expansion.

B. RV failure

1. Signs: Hypotension, possible suction events causing syncope or arrhythmias, and return of HF symptoms.
2. Echocardiography may demonstrate decreased RV function and enlarged RV dimensions.
3. Parameter changes encountered: Decreased pump flow and pump speed below fixed speed.
4. Suggested management: Consider inotropes, pulmonary vasodilators, volume expansion, ramped speed study, and mechanical right ventricular assist device.

C. Tamponade

1. Signs: Hypotension and decreased postoperative chest tube drainage.
2. Echocardiography may demonstrate focal or circumferential effusion causing tamponade physiology.
3. Parameter changes encountered: Decreased pump flow.
4. Suggested management: Pericardiocentesis or exploratory thoracotomy.

D. Hypertension

1. Signs: Typically asymptomatic.
2. Parameter changes encountered: Decreased pump flow and pump power and increased PI.
3. Suggested management: Increased afterload reduction and diuretics.

E. Volume overload

1. Signs: Edema.
2. Echocardiography to assess ventricular and valvular function.
3. Parameter changes encountered: Increased pump flow, pump power, and PI.
4. Suggested management: Consider adjustment of diuretics, fluid restriction, and ramped speed study.

F. Recurrent HF

1. Signs: Hypotension, pulmonary edema, and low cardiac index.
2. Echocardiography may demonstrate decreased RV and/or LV function. Valvular function should be assessed.
3. Parameter changes encountered: Decreased pump flow and PI.
4. Suggested management: Ramped speed study, adjustment of diuretics, RV function assessment, invasive hemodynamics, and treatment of HF symptoms.

G. Aortic insufficiency

1. Signs: Hypotension and return of HF symptoms.
2. Echocardiography shows dilated LV with severe aortic insufficiency.
3. Parameter changes: Increased pump flow with dilated LV.
4. Suggested management: Decrease pump speed to decrease the amount of aortic insufficiency. May eventually need aortic valve surgery.

H. Arrhythmia

1. Signs: Ventricular tachycardia on electrocardiogram, Holter, or telemetry. Syncope or presyncope.
2. Echocardiography may demonstrate intermittent suction events, worsened LV or RV function, and new valvulopathy.
3. Parameter changes: Decreased pump flow, pump power, and PI.
4. Suggested management: Ramped speed study and assess inflow cannula to ensure proper placement.

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Intraaortic Balloon Counterpulsation

- I. INTRODUCTION.** Intraaortic balloon counterpulsation (IABC) is usually used to **support hemodynamics** in cardiogenic shock and to **relieve medically refractory ischemia** in patients with severe coronary disease. The duration of support with an intraaortic balloon pump (IABP) is typically short, because multiple complications can develop in patients treated with IABC. Patients should be carefully selected for receiving IABC therapy and should be closely monitored in a critical care setting while the IABP is in place.

II. INDICATIONS

A. Cardiogenic shock

1. **Bridge to revascularization.** IABC provides temporary hemodynamic stabilization in patients with cardiogenic shock caused by acute myocardial infarction (MI). Hospital survival rates for cardiogenic shock with balloon pump support alone without revascularization are poor (5% to 20%). Early revascularization with percutaneous transluminal coronary angioplasty (PTCA) improves survival rates in cardiogenic shock caused by acute MI.
 - a. In the **Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries I (GUSTO I)** trial comparing fibrinolytic regimens for acute ST-segment elevation myocardial infarction (STEMI), PTCA was the only factor associated with a lower 30-day mortality rate in 2,972 patients with cardiogenic shock.
 - b. In addition, early placement of an IABP in this cohort of patients was associated with lower 30-day and 1-year mortality rates.
 - c. Cardiogenic shock and hemodynamic support during or after percutaneous coronary intervention are the primary reasons for IABP placement in more than half of all patients treated with IABC. IABP placement is an **ACC/AHA class I** recommendation in patients with STEMI presenting with cardiogenic shock when shock is not quickly reversed with pharmacologic therapy. The IABP in this setting is a stabilizing measure for angiography and prompt revascularization.
 2. **Bridge to a tertiary center.** Thrombolytic therapy alone in patients with cardiogenic shock is less successful than mechanical reperfusion. However, the addition of IABC to thrombolysis can improve outcomes in patients with cardiogenic shock. In 46 patients with acute MI and cardiogenic shock treated at community hospitals without angioplasty capabilities, simultaneous treatment with thrombolysis and IABC was associated with an improved 1-year survival rate (67% vs. 32%) and successful transfer to a tertiary facility for revascularization when thrombolysis failed.
- B. Acute MI treated with catheter-based reperfusion.** The **benefits** of IABC in patients with acute MI without cardiogenic shock treated with catheter-based reperfusion are **uncertain**.
1. In a randomized trial of 182 hemodynamically stable patients who underwent direct PTCA for acute MI, prophylactic IABC for 2 days after the procedure

- reduced recurrent ischemia and reocclusion of the infarct-related artery but had no effect on survival or reinfarction.
2. In the **Primary Angioplasty in Myocardial Infarction II (PAMI II)** trial, 437 high-risk patients (age > 70 years, multivessel coronary disease, reduced ejection fraction, vein graft disease, or persistent ventricular arrhythmias) treated with direct PTCA for acute MI were randomized to ± 1 to 2 days of IABC after PTCA. Patients treated with IABC had a slight reduction in recurrent ischemia but had no reduction in mortality, reinfarction, or infarct-related artery reocclusion. Thus, hemodynamically stable patients with acute MI treated with catheter-based reperfusion are not likely to benefit from IABP support after the intervention.
- C. High-risk percutaneous revascularization.** Patients at high risk for complications during percutaneous revascularization include those with unprotected left main coronary disease, left ventricular dysfunction (ejection fraction < 40%), the target vessel supplying > 40% of the myocardial territory, or severe congestive heart failure (CHF). Placement of an IABP in these high-risk patients affords the operator a longer duration of ischemia during balloon inflation and wire manipulation.
1. In a study of 219 patients undergoing unprotected left main trunk stenting, elective IABP placement was associated with fewer intraprocedural major adverse cardiac events, including combined end points of severe hypotension, MI, need for urgent bypass surgery, and death.
 2. Although there are no specific recommendations for when to use IABC during high-risk coronary interventions, improved percutaneous revascularization techniques with coronary stents and adjunctive glycoprotein IIb/IIIa receptor antagonists have reduced the need for prophylactic IABP placement in high-risk patients.
- D. Mechanical complications of acute MI.** **Acute mitral regurgitation (MR)** and **ventricular septal defect** are devastating complications of acute MI and frequently cause rapid deterioration progressing to cardiogenic shock. An IABP should be placed before surgical repair in patients with hemodynamically significant MR or ventricular septal defect after an MI. Placement of an IABP in the setting of STEMI and secondary acute mitral valve regurgitation is an **ACC/AHA class I** indication. Similarly, insertion of an IABP and prompt surgical referral are **class I** recommendations.
- E. Refractory unstable angina.** Patients with severe coronary disease who have refractory ischemia or hemodynamic instability show **dramatic improvement** when IABC is used before revascularization. The ACC/AHA clinical guidelines assign a **class I** recommendation in STEMI patients and a **class IIa** recommendation in Unstable angina/Non ST segment elevation myocardial infarct (UA/NSTEMI) patients for IABP placement in the setting of severe ischemia that is continuing or recurs frequently despite intensive medical therapy. In the setting of STEMI, refractory pulmonary congestion carries a **class IIb** recommendation for IABP placement.
- F. Weaning from cardiopulmonary bypass/postoperative pump failure.** Patients with severe left ventricular dysfunction or those with prolonged runs on cardiopulmonary bypass can be difficult to wean from bypass after open heart surgery because of stunned myocardium from prolonged cardioplegic arrest. For these patients, IABP support improves hemodynamics and facilitates weaning from cardiopulmonary bypass.
- G. End-stage cardiomyopathy/bridge to cardiac transplantation.** An IABP improves cardiac output and lowers filling pressures in patients with dilated and ischemic cardiomyopathy. It can be used for hemodynamic support before cardiac transplantation.
1. **Disadvantages** of prolonged IABP support in patients awaiting cardiac transplantation include a high risk of infection and the need for continuous bed rest.
 2. However, with improved inotropic therapy and implantable left ventricular assist devices for patients awaiting cardiac transplantation, IABC is now used infrequently for prolonged mechanical support in patients with end-stage cardiomyopathy.

- H. Refractory ventricular arrhythmias.** Incessant ventricular tachycardia compromises left ventricular filling, reduces stroke volume, and causes or exacerbates ischemia. IABC improved hemodynamics, lessened ischemia, and controlled refractory ventricular arrhythmias in 86% of patients in a large case series. Placement of an IABP support in patients with STEMI and refractory polymorphic ventricular tachycardia carries an **ACC/AHA class IIa** recommendation.
- I. Support during noncardiac surgery.** Patients with severe coronary disease, recent MI, and severe left ventricular dysfunction are at high risk for cardiac complications when they undergo noncardiac surgery. Case reports have demonstrated that high-risk patients are stabilized hemodynamically and have acceptable postoperative outcomes when prophylactic IABP support is used during and after noncardiac surgical procedures.
- J. Decompensated aortic stenosis** can be managed with temporary IABP support to improve the stroke volume and reduce the transvalvular gradient before aortic valve replacement. In a study of 25 patients with severe aortic stenosis and cardiogenic shock, IABP support was associated with prompt improvement in cardiac output and filling pressures, allowing stabilization of patients before surgery. However, because aortic insufficiency often accompanies severe aortic stenosis, careful monitoring early after initiation of IABC is recommended to ensure that aortic insufficiency is not worsened by the balloon pump.

III. CONTRAINDICATIONS

- A. Aortic dissection.** Any type of aortic dissection precludes IABP use because of the potential of the balloon catheter to extend the dissection and to worsen ischemia of a peripheral vascular bed that may be involved by the dissection.
- B. Abdominal or thoracic aneurysm.** Using IABP with an abdominal or thoracic aneurysm can precipitate an acute aortic dissection, dislodgement of atheroemboli, or aortic rupture, so the presence of an aneurysm is a contraindication to IABP use.
- C. Severe peripheral vascular disease**
1. The majority of the complications of IABC are caused by vascular insufficiency in the accessed leg because of the **large size of the balloon sheath and catheter and the concomitant presence of peripheral vascular disease** in patients who typically need IABC. In the past, the IABP catheters had been available only in 8F and 9.5F sizes; however, with improving equipment, 7F catheters have been introduced, and these have diminished the rate of complications due to obstruction of arterial flow.
 2. **Limb ischemia and threatened limb viability** can occur when peripheral perfusion is compromised by the balloon catheter and sheath. The IABP catheter can be inserted without a sheath to reduce the diameter of obstruction in the iliac vessels, but in patients with tortuous aortoiliac vessels, sheathless IABP insertion can be difficult.
 3. Thus, severe peripheral vascular disease is a contraindication to IABP insertion, depending on the necessity of IABP support and the degree of vascular compromise.
- D. Descending aortic and peripheral vascular grafts**
1. **Prosthetic descending aortic grafts and iliofemoral vascular grafts** are relative contraindications to IABC. Consultation with a vascular surgeon is recommended before attempting balloon pump insertion in these patients.
 2. **Iliac artery stents** are not an absolute contraindication to IABP placement. However, passage of the guidewire and balloon catheter through the stent must be performed under direct fluoroscopic guidance.
- E. Coagulopathy or contraindication to heparin**
1. The balloon catheter is thrombogenic, and intravenous heparin is commonly given while the IABP is in place to prevent the development of thrombi on the balloon surface. Patients with a contraindication to heparin, such as those with prior heparin-induced thrombocytopenia, can be **anticoagulated with alternative agents** such as direct thrombin inhibitors like bivalirudin.

2. After cardiac surgery, heparin can be avoided because of the increased risk of intrathoracic bleeding, but IABP support in such patients is usually of short duration. In nonsurgical patients, if an anticoagulant cannot be given or if a severe coagulopathy exists that could precipitate bleeding at the access site, IABC is discouraged, but it could safely be undertaken for a short period.
- F. Moderate to severe aortic insufficiency.** By inflating during diastole, the IABP can worsen aortic insufficiency when blood is displaced to the proximal aorta. No consensus exists as to what degree of aortic insufficiency absolutely contraindicates IABP use. Therefore, **careful monitoring** of patients with aortic insufficiency who absolutely need IABP support is recommended.

IV. HEMODYNAMICS OF BALLOON PUMP FUNCTION

A. Decreased afterload

1. As systole begins, the intraaortic balloon rapidly deflates and creates a negative pressure in the aorta, which reduces afterload and improves forward flow from the left ventricle. Afterload reduction occurs because the aortic end-diastolic pressure is reduced, resulting in an increase in cardiac output of approximately 20% and a decrease in the mean pulmonary capillary wedge pressure of approximately 20%.
2. The **overall hemodynamic benefit** of IABP appears to be a reduction in left ventricular wall stress from decreased filling pressures and decreased afterload, which in turn improves stroke volume and cardiac output (see Figs. 63.1 and 63.2).

B. Augmented coronary perfusion

1. When the balloon inflates during diastole, it displaces blood to the proximal aorta and augments aortic diastolic pressure and, thus, coronary perfusion pressure. The augmentation of coronary perfusion pressure is more dramatic when systemic hypotension is present (see Figs. 63.1 and 63.2).

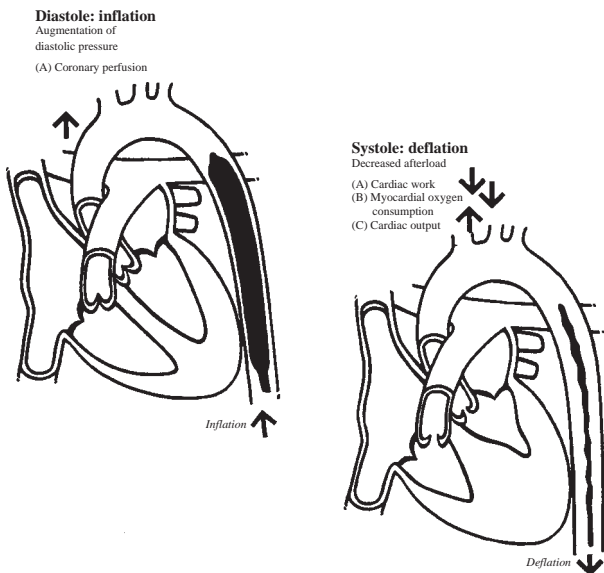


FIGURE 63.1 By inflating during diastole, the intraaortic balloon pump increases coronary perfusion. Deflation of the balloon at the onset of systole decreases myocardial wall stress and oxygen demand and increases cardiac output. Courtesy of Datascope Corp.

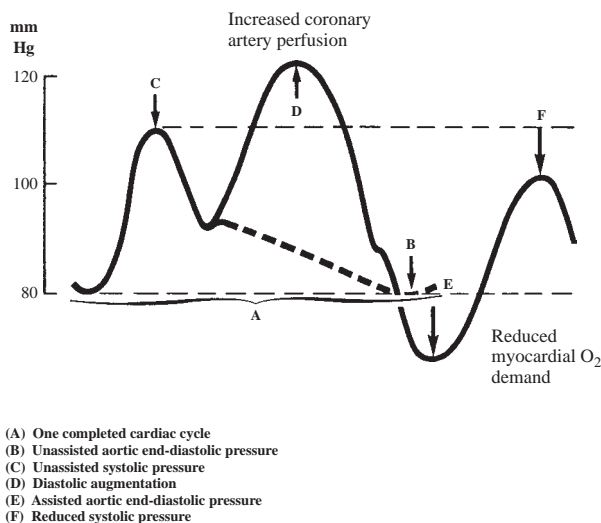


FIGURE 63.2 Proper timing of balloon function occurs when the balloon inflates on the downslope of the systolic pressure waveform and deflates before the onset of the next systolic waveform. The intraaortic balloon pump inflation in diastole increases diastolic pressure to improve coronary artery perfusion and to increase mean arterial pressure. In addition, aortic end-diastolic pressure is reduced when the balloon deflates in end-diastole to lower afterload and myocardial oxygen demand. Courtesy of Datascope Corp.

2. Doppler flow studies have demonstrated that peak coronary flow velocity is increased with IABP support, but there is no improvement in coronary flow past critical coronary stenoses (unless the obstructions are first relieved with percutaneous revascularization). Also, collateral coronary flow does not increase with IABP support. Thus, with severe, nonrevascularized coronary disease, IABP relieves ischemia more through decreased left ventricular wall stress and decreased myocardial oxygen demand than through increased coronary perfusion.

V. INSERTION TECHNIQUE/PATIENT EVALUATION AND MONITORING

- A. **Balloon sizing** is based on the patient's height. Four common balloon sizes are available: 50 cm³ for patients taller than 6', 40 cm³ for patients between 5' 4" and 6', 34 cm³ for patients between 5' and 5' 4", and 25 cm³ for patients shorter than 5'. Balloon length and diameter increase with each larger size. The 40-cm³ balloon is most commonly used, whereas the 50-cm³ balloon is rarely used because the balloon is too long for most patients.
- B. **Evaluating peripheral vasculature.** Proximal and distal pulses are assessed in both legs, and ankle/brachial indices can also be determined. The leg with the strongest pulses and/or the best ankle/brachial index score should be chosen for access.
- C. **Insertion technique**
 1. **Gaining access/sheath insertion.** After careful evaluation of clotting parameters and peripheral vasculature, the leg chosen for access should be shaved and prepped with antiseptic solution from the umbilicus to the knee. After infiltration with a local anesthetic, the femoral artery is accessed with an 18G introducer needle, and a 0.030" × 145 cm J-tipped guidewire is advanced through the needle to the aortic arch under **fluoroscopic guidance**. A smaller 5F dilator

is first inserted over the wire to dilate the subcutaneous tissues. Then the sheath, loaded with a larger dilator that is 1F smaller than the sheath, is inserted over the guidewire. The guidewire should be left in place in the aortic arch.

2. **Balloon insertion.** The two commonly available balloon catheter sizes are 8F and 9.5F. A 7F- and 7.5F-sized catheter and sheath have become available but pertinent data regarding their use are still limited. The prewrapped balloon is inserted over the guidewire and is advanced until the proximal tip is positioned 1 cm below the left subclavian artery and 2 cm above the carina. The guidewire is then removed, and the distal tip of the balloon is visualized under fluoroscopic guidance to ensure that it is out of the sheath.
3. **Insertion without fluoroscopy guidance.** Fluoroscopic guidance is recommended for placement of the IABP. However, if fluoroscopy is unavailable, the distance from the angle of Louis to the umbilicus and then to the common femoral artery insertion site is measured to determine the approximate distance the balloon must be advanced.
4. **Surgical insertion**
 - a. Occasionally, balloon pumps can be inserted surgically **by directly exposing the common femoral artery** or by suturing a 6- to 12-mm prosthetic graft end-to-side to the femoral artery to provide a conduit for the catheter. Distal limb ischemia is reduced with these methods, but grafts must be removed surgically, and the femoral artery has to be directly repaired after IABP removal when surgical access is used.
 - b. Balloon pumps can also be directly inserted into the ascending or thoracic aorta **during open heart surgery.**
5. **Difficulties with access.** If passage of the guidewire is difficult, a 5F sheath can be placed in the common femoral artery. Then the contrast medium can be injected through the sheath or through a pigtail catheter to define the iliofemoral anatomy.
 - a. If severe iliac or femoral artery obstruction is demonstrated, the balloon can be inserted on the contralateral side, the obstructions can be treated with peripheral angioplasty and stenting before balloon insertion, or the procedure can be aborted.
 - b. If severe obstruction or aneurysmal dilatation of the distal abdominal aorta is demonstrated, the balloon catheter should not be inserted.
6. **Sheathless insertion.** In patients with peripheral vascular disease, the balloon catheter can be inserted without a sheath, directly over the guidewire, after appropriate dilatation of the subcutaneous tissue. Retrospective reviews have shown that lower limb ischemia is reduced with this technique. However, a sheathless balloon catheter cannot be repositioned once placed and has a greater potential to become infected from skin flora than a sheathed balloon catheter. Smaller balloon catheters and stiffer guidewires are being developed to aid in sheathless insertion.
7. **Tortuous iliofemoral vessels**
 - a. When the tortuosity of the iliofemoral vessels prevents passage of the 0.030" guidewire supplied in the IABP kit, a 0.035" Wholey wire can be used to traverse the tortuous vessels. A long (45 or 60 cm) flexible sheath is then placed in the descending aorta past the tortuous iliac vessels.
 - b. A superstiff 0.038" wire is then exchanged through the sheath. The 11" IABP sheath is inserted over the superstiff wire, which provides more support for placement of the less flexible IABP sheath. The superstiff wire is then exchanged for the 0.030" standard IABP wire through the sheath, and the balloon catheter is inserted over this wire into the proper position.

D. Initial setup

1. After insertion, the helium gas line of the balloon catheter is connected to the IABP console, and the central lumen of the catheter is attached to an arterial pressure monitor device on the console with pressure tubing, after allowing the line to backbleed.
2. Balloon autoinflation is initiated from the console, the arterial line attached to the central lumen of the catheter is flushed, and the initial IABP inflation is at 1:2 (per cardiac cycle) while the timing is adjusted (Section VI).

3. Balloon inflation is then observed under fluoroscopic guidance to ensure that the balloon is completely out of the sheath. If the balloon is kinked or is not inflating fully, it should be repositioned by pulling the sheath back a few inches or it should be manually inflated.
4. Finally, the sheath and balloon catheter are sutured in place, dressed using sterile technique, and the inflation is changed to 1:1.

E. Monitoring

1. A **chest x-ray film is immediately obtained** after IABP placement to verify the catheter position, even if fluoroscopic guidance has been used.
2. **Intravenous heparin** is started once the balloon and sheath are secure to maintain the activated partial thromboplastin time at 50 to 70 seconds.
3. **Daily chest x-ray films** are recommended while the IABP is in place so that the physician can check the position of the catheter. If the catheter needs to be repositioned, it can be manipulated through a sterile plastic sleeve placed over the part of the catheter that extrudes from the sheath while the balloon is placed on standby mode.
4. Daily hemoglobin and platelet counts are followed to monitor for hemolysis and thrombocytopenia.

F. Care of the patient with an IABP

1. All patients with an IABP in place should be closely observed in a **critical care setting. The patient should be kept supine in bed**, and peripheral pulses should be regularly evaluated for **possible limb ischemia** (dorsalis pedis/posterior tibial pulses should be checked every 6 to 8 hours with use of Doppler if necessary).
2. **The accessed leg should be secured** to prevent inadvertent or involuntary movement by the patient.
3. **Use of prophylactic antibiotics is not recommended** while the IABP is in place.
4. **Blood samples generally should not be obtained from the central lumen of the IABP** because the risk of clotting the lumen is increased, and air or small thrombi can be injected through the central lumen during flushing of the tubing after blood withdrawal.

VI. BALLOON PUMP TRIGGERING AND TIMING

A. Triggering.

Balloon pump inflation can be triggered by the surface electrocardiogram (ECG), the arterial pressure waveform, a paced rhythm, or an internal asynchronous mode.

1. Preferably, the surface ECG is used to trigger IABP inflation, which is appropriately delayed after the R wave to begin at the time in the cardiac cycle when the aortic valve closes (dicrotic notch).
2. If the IABP fails to trigger properly from the surface ECG, change the lead being evaluated, check surface electrode placement, or increase the QRS gain on the console monitor.
3. For patients with poor surface electrocardiographic tracings, the balloon can be triggered from the central arterial pressure waveform. Pacing spikes should be used to trigger the balloon in patients who are 100% paced.
4. When the patient is arresting or when the other triggering mechanisms are not working correctly, an internal asynchronous mode can be used to trigger the balloon to inflate at a regular interval.

B. Timing.

Ideal balloon pump timing occurs when the balloon inflates on the downslope of the systolic pressure waveform before the dicrotic notch and deflates before the onset of the next systolic pressure waveform (see Fig. 63.2). Timing is usually adjusted manually, but it can be automatically adjusted by internal algorithms programmed in the console.

1. **Early inflation** (see Fig. 63.3) is defined as inflation of the IABP before aortic valve closure (dicrotic notch).

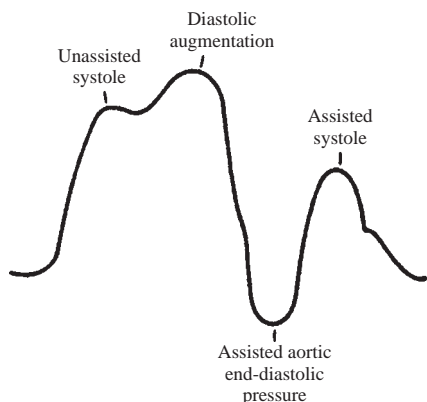


FIGURE 63.3 With early balloon inflation, the aortic valve closes prematurely, and left ventricular wall stress and myocardial oxygen demand are increased. Courtesy of Datascope Corp.

- a. There is premature closure of the aortic valve with increased afterload, left ventricular wall stress, and myocardial oxygen demand. Stroke volume is decreased.
- b. It is corrected by delaying inflation until after aortic valve closure.
2. **Late inflation** (see Fig. 63.4) is defined as inflation of the IABP well after closure of the aortic valve.
 - a. There is diminished diastolic pressure augmentation and suboptimal coronary perfusion.
 - b. It is corrected by adjusting inflation to occur just before the dirotic notch.
3. **Early deflation** (see Fig. 63.5) is defined as deflation of the IABP before isovolumic left ventricular contraction.
 - a. There is suboptimal diastolic augmentation, coronary perfusion, and afterload reduction, which then lead to increased myocardial oxygen demand.
 - b. It is corrected by delaying deflation until just before the onset of systole.
4. **Late deflation** (see Fig. 63.6) is defined as deflation of the IABP after the onset of systole.
 - a. There is impaired left ventricular emptying, increased afterload and preload, increased myocardial oxygen consumption, and reduced stroke volume.
 - b. It is corrected by adjusting deflation to occur just before the onset of systole.

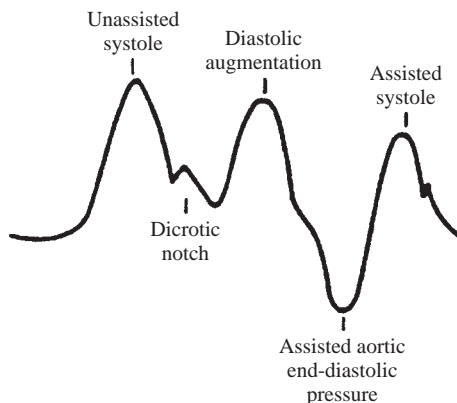


FIGURE 63.4 With late balloon inflation, there is suboptimal augmentation of diastolic aortic pressure and coronary perfusion. Courtesy of Datascope Corp.

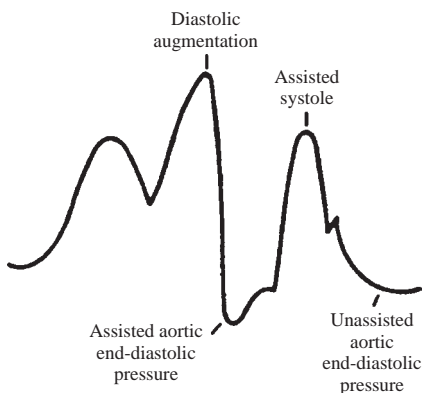


FIGURE 63.5 With early balloon deflation, there is suboptimal augmentation of coronary perfusion and afterload reduction. Courtesy of Datascope Corp.

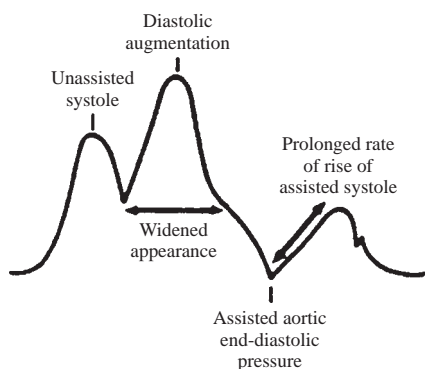


FIGURE 63.6 With late balloon deflation, there is no afterload reduction, and myocardial oxygen consumption is increased. Courtesy of Datascope Corp.

5. **During arrhythmias.** Adequate augmentation with the balloon pump is difficult to achieve with tachyarrhythmias. When heart rate approaches 150 beats/min, there is insufficient time for the helium gas to shuttle in and out of the balloon with each inflation. With rapid atrial fibrillation, variable systolic pressure waveforms caused by inadequate left ventricular filling and rapid pulse rates make augmentation especially difficult. Adjusting balloon inflation to 1:2 can sometimes improve augmentation with tachyarrhythmias.
- C. **Troubleshooting.** In the situation of **console alarms**, there may be the following problems:
 1. **Loose connections** in the gas drive line or arterial pressure tubing.
 2. **Blood in the tubing.** If blood is detected in the gas drive lumen, put the balloon catheter on standby and evaluate for balloon rupture or entrapment (Section VII).
 3. **Poor augmentation**
 - a. Adjust the timing.
 - b. Change the triggering mechanism (Section VI.A).
 - c. Evaluate inflation/deflation of the balloon and the catheter position under fluoroscopic guidance to detect balloon kinking.
 - d. If the IABP is thought to be positioned in a false lumen of the aorta because of poor augmentation, 10 to 20 mL of contrast media can be injected through the central lumen of the catheter to evaluate the position under fluoroscopy.

VII. COMPLICATIONS

A. Vascular. Common vascular complications of IABP include limb ischemia, hematoma around the access site, and bleeding from the access site. Rates of vascular complications have varied in the literature from 5% to 20%, depending on the patient populations studied. However, a contemporary series showed the incidence of limb ischemia to be 2.3% and incidence of major limb ischemia to be 0.5% in 5,495 consecutive patients with IABP. Diabetes, female sex, preexisting peripheral vascular disease, history of smoking, and catheter size are all independent risk factors that are strongly associated with the development of ischemic vascular complications from IABP use.

1. Ischemia

- a. If ischemia develops in the accessed leg, the balloon catheter and sheath should be removed and hemostasis obtained at the access site.
- b. If ischemia is still present, consultation with a vascular surgeon is indicated. Surgical intervention for ischemic limbs caused by IABP catheters includes thrombectomy, surgical bypass grafting, and, rarely, amputation.

2. Bleeding

- a. Bleeding around the access site develops in 1% to 5% of patients treated with IABP. It is usually controlled with prolonged manual pressure at the access site.
- b. Hematomas that develop at the access site may require transfusion of blood products and, occasionally, direct arterial repair.
- c. Pseudoaneurysms after IABP removal are rare but often require surgical correction.

B. Infection. Infectious complications are rare and include access site infections, catheter infections, and bacteremia. No studies have addressed how frequently balloon catheters become infected and how frequently they need to be changed to limit infectious complications.

C. Balloon rupture should be considered if blood is detected in the gas drive line lumen or if balloon augmentation ceases.

1. Small leaks in the balloon can develop from damage to the balloon surface caused by inflation against calcified aortic plaques. Rates of balloon leak can be as high as 4.2%.
2. *Potential complications for the patient include helium gas embolism and balloon entrapment when blood leaks into the balloon, clots, and prevents adequate deflation of the balloon for removal.*
3. Use of standard-sized balloons (40 cm³) in patients shorter than 170 cm (5'6") is associated with balloon rupture. This is thought to be caused by damage to the balloon when inflation occurs in the smaller and more plaque-laden distal abdominal aorta. Thus, a 34-cm³ balloon should be used in patients shorter than 170 cm.

D. Balloon entrapment occurs when balloon rupture causes a clot to form within the balloon, preventing deflation during removal. When resistance is encountered during balloon catheter removal, balloon entrapment should be considered and fluoroscopy immediately carried out to assess the position of the retained catheter.

1. Management of balloon entrapment usually involves surgical extraction because forceful removal of a partially deflated balloon catheter could cause serious vascular injury.
2. Case reports have documented successful lysis of clots within the balloon by instilling thrombolytic agents through the gas drive lumen of the IABP catheter. The balloons were deflated after clot lysis and the catheters successfully removed.

E. Red blood cell and platelet destruction. Due to the shear forces of the balloon catheter, hemolytic anemia and mild thrombocytopenia can occur during IABP support. Daily hemoglobin and platelet values should be checked. Platelet counts < 50,000 are unlikely to be caused by the IABP and alternative causes should be sought.

F. Other complications. Rare complications of IABP use include acute renal failure, mesenteric ischemia, and paraplegia from plaque embolization leading to

thrombosis of the renal, mesenteric, or spinal arteries, respectively. Aortic dissections and aortic perforations, though rare, usually occur during insertion.

VIII. REMOVING THE IABP CATHETER

A. Weaning. Whether IABC needs to be weaned before the balloon catheter is removed depends on multiple factors, including the duration of the support, the hemodynamic status of the patient, and left ventricular function.

1. The usual practice is to change IABP inflation to 1:2 for a few hours and then to 1:3 with close hemodynamic monitoring.
2. At the same time, intravenous inotropic drugs are used to simulate the IABP's hemodynamic effects. Dobutamine or milrinone is used to maintain an adequate cardiac output, and nitroprusside is used to replace the afterload reduction provided by the IABP.
3. If weaning is tolerated hemodynamically, the balloon can then be removed.

B. Withdrawal of the balloon catheter and sheath

1. Intravenous heparin should be discontinued for at least 4 hours before removal of the catheter. The activated coagulation time is checked until it falls below 150 seconds or partial thromboplastin time normalized.
2. Percutaneously placed catheters can then be removed manually, but surgically placed catheters must be removed with direct arterial repair.
3. To begin removal of the balloon catheter, the balloon is changed to standby and the gas drive line is disconnected. Then, the balloon catheter is pulled back until resistance is met, indicating that the catheter is in the sheath. The sheath and the balloon catheter are then withdrawn together as a unit, but excessive force should never be applied.

C. Hemostasis

1. After the balloon is withdrawn, the puncture site is allowed to backbleed for 1 to 2 seconds while pressure is held distal to the puncture site to evacuate proximal thrombi.
2. Then manual pressure is applied proximal to the puncture site, and backbleeding is repeated to evacuate distal thrombi.
3. Manual pressure is then applied for 30 to 45 minutes over the puncture site until adequate hemostasis is achieved.
4. A compressive dressing is applied thereafter.

D. Monitoring during IABP removal

1. During the application of manual pressure to the puncture site, the distal pulses in the leg should be continually assessed, and pressure should be adjusted to maintain adequate distal perfusion.
2. The patient should be confined to strict bed rest for 6 to 12 hours after the catheter and sheath have been removed, and the leg should be periodically assessed for signs of ischemia.

IX. CHANGING THE IABP CATHETER

A. Reasons for changing the IABP

1. When patients require prolonged IABP support, some clinicians change the catheter and sheath every 4 to 5 days to prevent infectious complications. However, there is no consensus on using this approach.
2. Other reasons for changing the IABP include balloon entrapment and rupture, kinking of the catheter or sheath (which prevents adequate balloon inflation), or fever (which may indicate bacteremia from a line infection).

B. Simultaneous change. In patients who are critically dependent on IABP support and who need the IABP changed for one of the above reasons, the catheter and sheath must be changed simultaneously with placement of a new IABP.

1. Contralateral femoral artery

- a. When the contralateral femoral artery can be used, it is accessed and the sheath is placed. A guidewire is then positioned in the aortic arch while the old balloon is on standby.
- b. Counterpulsation is reinitiated, and the new balloon catheter is prepared and readied for use.
- c. The old balloon is then deflated and quickly withdrawn, while the new balloon catheter is placed over the guidewire from the contralateral femoral artery. This technique limits the period without IABP support during the change to < 30 seconds.
- d. Anticoagulation can safely be discontinued before and after a simultaneous change to aid in achieving hemostasis at the old access site.

2. Same femoral artery

- a. When the contralateral femoral artery cannot be used, the old catheter and sheath must be removed and changed under direct vision.
- b. The accessed femoral artery is exposed surgically, and a purse-string suture is placed around the preexisting sheath.
- c. The old sheath is then removed, and tension is applied to the suture for hemostasis.
 - (1) The small dilator in the catheter package is directly inserted into the previous puncture site, and the guidewire is advanced to the aortic arch through it.
 - (2) The sheath is advanced over the guidewire into the proper position, and the purse-string suture is tied down.
 - (3) The balloon catheter is then inserted via the sheath, and the soft tissue and skin incision are closed with sutures.
- d. In emergency situations, the preexisting sheath can be rewired and a new balloon catheter inserted through the old sheath. However, infectious complications are high with this approach.

ACKNOWLEDGMENTS: *The author thanks Dr. Apur R. Kamdar and Dr. Matthew T. Roe for their contributions to earlier editions of this chapter.*

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CHAPTER

64

Andrew N. Rassi

Left Heart Catheterization

- I. INTRODUCTION.** In 1958, Dr. Mason Sones and colleagues at the Cleveland Clinic performed the first selective coronary arteriographic procedure. Since then, left heart catheterization (LHC) has become an important tool in diagnostic cardiology. More than 1.5 million cardiac catheterizations are performed yearly in the United States. Despite the advent of other imaging modalities, coronary arteriography remains the clinical gold standard for determining the presence of significant coronary artery disease (CAD).

LHC is an invasive procedure with serious potential risks. To be competent in LHC, a cardiologist-in-training must perform at least 300 catheterizations, serving as primary operator on 200. During training, the operator must be supervised by a cardiologist who is already competent in the procedure. Because there is the ability to treat a lesion with percutaneous intervention at the same time as the diagnostic angiogram, it is important to have a plan regarding how to use the information obtained.

II. INDICATIONS. The American College of Cardiology and the American Heart Association (ACC/AHA) have categorized reasonable indications for LHC as class I, when there is consensus that LHC is indicated, or class II, when there is no consensus that LHC is indicated, but nonetheless the procedure is frequently performed (see Table 64.1).

A. Acute myocardial infarction (MI). LHC is given a class I indication for routine use in acute MI, particularly in those who will likely undergo primary percutaneous cardiac intervention, those in cardiogenic shock or with other evidence of hemodynamic instability, or those with mechanical complications who are likely to undergo surgical repair. It can be used with the goal of performing primary angioplasty in patients with acute ST-segment elevation MI. There is evidence of the benefit of an early invasive strategy in stable patients with non-ST-segment elevation MI. In patients with non-ST-segment elevation MI, an early invasive strategy has received a class I indication in the presence of the following risk features: elevated cardiac troponins, new or presumed new ST-segment depression, heart failure (HF), depressed ventricular function, hemodynamic instability, sustained ventricular tachycardia, previous bypass surgery, and previous coronary intervention in the last 6 months. Patients with persistent pain or unresolved electrocardiographic changes after thrombolytic therapy are also class I candidates for LHC. Routine LHC soon after thrombolytic therapy in a patient who appears to have clinically reperfused is a class IIb indication.

B. Unstable angina. LHC is given a class I indication in the patient with refractory unstable angina that cannot be controlled by medical therapy. Its role in unstable angina that can be medically controlled is controversial.

C. Chronic stable angina. LHC is given a class I indication for purposes of revascularization in chronic stable angina for patients whose angina is poorly controlled by medicines or who are intolerant of antianginal medications.

D. Abnormal stress test. A stress test that is positive at a low work load (6.5 metabolic equivalents of oxygen consumption) or that is classified as high risk is a class I indication for LHC. An ST depression of 2 mm, especially in multiple leads or persisting into recovery 6 minutes, an ST elevation of 2 mm in leads without Q waves, a drop in blood pressure of > 10 mm Hg with exercise, or development of ventricular tachycardia with exercise constitutes a high-risk stress test. A high-risk stress test on a concomitant imaging modality showing left ventricle dilatation, a drop in ejection

TABLE 64.1 Indications and Contraindications to Left Heart Catheterization

Indications ^a	Contraindications ^a
<ul style="list-style-type: none"> - Acute myocardial infarction - Unstable angina - Chronic stable angina, uncontrolled by medications - Abnormal stress test - Ventricular arrhythmias - Left ventricular dysfunction - Valvular heart disease - Preoperative coronary assessment for cardiovascular surgery - Preoperative risk assessment for noncardiovascular surgery - Periodic follow-up after cardiac transplantation 	<ul style="list-style-type: none"> - Active bleeding - Coagulopathy - Acute or chronic renal failure - Active infection - Severe anemia - Electrolyte abnormalities - Inability to lie supine (i.e., decompensated heart failure) - Malignant hypertension - Extensive comorbidities—risk of revascularization likely outweighs the benefit - Patient unable to cooperate or does not desire procedure

^aSee text for full details.

fraction of 10%, or multiple areas of ischemia is a class I indication for catheterization. These indications hold true even if the patient is asymptomatic. Positive stress tests without high-risk criteria are class II indications for LHC.

- E. Ventricular arrhythmia.** A history of sustained polymorphic ventricular tachycardia, without obvious metabolic cause, is considered a class I indication for LHC.
- F. Left ventricular dysfunction.** LHC can provide an estimate of left ventricular function and regional wall motion. Left ventricular dysfunction of unknown cause, with an ejection fraction of $< 40\%$, is a class I indication for LHC to rule out CAD.
- G. Valvular heart disease.** LHC can be performed to assess the severity of outflow tract obstruction (aortic stenosis and hypertrophic obstructive cardiomyopathy). It can also help quantify aortic and mitral regurgitation (MR). With the advancements in Doppler and color echocardiography, the major role of cardiac catheterization is to provide confirmatory data and to rule out CAD as part of the operative workup. LHC has a class I indication in patients requiring valve surgery who are at risk for CAD. Most centers perform LHC before valve surgery in those older than 50 years to rule out clinically silent CAD. Younger patients may require LHC if cardiac risk factors are present or if coronary reimplantation may be needed as part of the surgery (homograft implantation, ascending aorta replacement, or Ross procedure).
- H. Preoperative.** LHC is performed before ascending aortic aneurysm surgery or some cases of ascending aortic dissection surgery. It is also performed on patients with congenital heart disease to evaluate lesions such as ventricular septal defects and to rule out concomitant coronary anomalies or atherosclerotic disease, if symptomatic. In patients with angina or a positive stress test who are to undergo high-risk surgery, LHC is given a class I indication.

III. CONTRAINDICATIONS. The following are relative contraindications to LHC (see Table 64.1).

- A. Coagulopathy.** Coagulopathy must be corrected before elective catheterization. The usual recommendation for patients on warfarin (Coumadin) is to discontinue it 72 hours before the procedure. In elective cases, an international normalized ratio of < 1.8 is a cutoff that is often used. If the patient is heparinized, this is usually stopped 2 hours before the procedure. A platelet count of $< 50,000$ substantially increases the risk of bleeding. After thrombolytic therapy, bleeding is more likely and elective catheterization is best deferred. However, if the indication for the procedure is urgent, it is possible to proceed with caution, with blood products kept ready for support as needed. Antecedent glycoprotein IIb/IIIa inhibitor therapy poses much less of a risk. Body habitus is also a factor in deciding what level of anticoagulation is acceptable before a catheterization. Obesity increases the chances of bleeding (if multiple attempts at access are needed) and makes bleeding more difficult to detect. Finally, the availability of closure devices makes it possible to seal the artery after the procedure.
- B. Renal failure.** A rising creatinine is generally a reason to defer elective cardiac catheterization. In a patient on dialysis, catheterization is generally timed immediately after the dialysis. In a patient with stable but moderately severe renal failure, catheterization may be performed with an awareness of the increased risk of needing dialysis.
- C. Dye allergy.** A history of allergy to previous contrast administration should be sought. Although an allergy to shellfish and seafood has been linked to contrast reactions in some studies, other studies dispute such a relationship. Individuals with a history of asthma or atopy are at increased risk of developing contrast allergies. Treatment of patients with a history of dye allergy is described in Section **IV.F.2**.
- D. Infection.** Active infection is a reason to defer elective cardiac catheterization. Local skin infection at the site of the potential puncture is also undesirable. Fungal infection in groin creases should be controlled before elective cardiac catheterization by the femoral approach; this is a particular concern in obese patients. Alternatively, LHC may be performed through a brachial or radial approach in patients with fungal infection in groin creases.

- E. Laboratory abnormalities.** Severe anemia, hypokalemia, or hyperkalemia should be corrected before the elective procedure. In the presence of digitalis toxicity, elective catheterization is best deferred.
- F. Decompensated HF.** Severe HF raises the risks of cardiac catheterization. It is best to optimize medical therapy before elective catheterization. At a minimum, the patient should be able to lie supine without respiratory insufficiency.
- G. Severe peripheral vascular disease.** Symptoms of claudication warrant careful assessment of pulses. An inadequate lower extremity pulse favors an upper extremity approach. A synthetic vascular graft that is older than 6 months is not a strict contraindication to catheterization, but special care should be taken in gaining access as well as in obtaining hemostasis. However, the risk of embolization of friable athroma or thrombus is heightened, and this risk increases with the age of the graft.
- H. Abdominal aortic aneurysm (AAA).** Presence of an AAA requires special care during a cardiac catheterization (see subsequent text). An arm approach obviates the need to cross the AAA altogether.
- I. Uncontrolled severe hypertension.** Blood pressure should be controlled before elective cardiac catheterization to maximize the safety of the procedure. In particular, severe bleeding can occur at the access site after sheath removal if the patient is very hypertensive, especially if above 180/100 mm Hg.

IV. PATIENT PREPARATION

- A. Informed consent.** A detailed discussion with the patient (and family) should outline the indication for the procedure, as well as the alternative treatment and diagnostic options. Specific mention of the serious risks of complications, such as death, MI, stroke, arrhythmia, bleeding, radiation exposure, and kidney failure, must be made (see complications in subsequent text). The possible need for emergency coronary artery bypass grafting (CABG) should be noted. The risk of serious complications should be individualized. Informed consent should be documented in the medical record.
- B. Precatheterization assessment.** Before proceeding with an LHC, a detailed clinical assessment is necessary, including a comprehensive history and physical examination. All peripheral pulses should be palpated, and arterial bruits, if any, should be documented before the catheterization as a baseline for future reference. In addition, laboratory data, including a comprehensive metabolic panel, complete blood count, and coagulation studies, should be obtained for all patients. Abnormalities in the laboratory parameters, if any, should be addressed before proceeding with LHC.
- C. Medications.** If percutaneous coronary intervention is likely, pretreatment with aspirin 325 mg by mouth (PO) should be given before the catheterization, as it has been shown to improve outcomes with angioplasty. If stenting is a strong possibility, clopidogrel 300 mg PO should be given as a loading dose before the procedure. Metformin should be stopped at the time of the procedure, although the risk of lactic acidosis is extremely low in a patient with normal creatinine.
- D. Education.** Patients should be warned that they might feel a hot sensation lasting about 30 seconds due to the injection of ionic contrast dye. Some patients may also feel nauseated. Patients should be specifically instructed to cough when they hear anyone in the room say "cough." This maneuver accelerates resolution of dye-induced bradycardia.
- E. Equipment.** Before performing a cardiac catheterization, it is essential to ensure that the monitoring equipment is fully functional. Continuous electrocardiographic monitoring of heart rate (HR), rhythm, and ST segments, an automated blood pressure cuff, and continuous pulse oximetry are mandatory. Resuscitation equipment should be tested and ready. In particular, defibrillators and intubation trays must be available next to the patient. If a long procedure is anticipated, many operators prefer placement of a Foley or Texas urinary catheter. Before actually beginning the procedure, the fluoroscopy and cine equipment should be tested by taking a picture

of the patient's nameplate. The usual frame rate of cine film is set at 30 frames/s; 60 frames/s can be useful for patients with tachycardia. In thin individuals who are bradycardic (< 60 beats/min), the frame rate can be lowered to 15 frames/s. In addition, the table should move freely to the level of the patient's groin.

F. Contrast dye

1. **Choice of contrast.** Ionic contrast dye was historically used during most cardiac catheterizations. In most circumstances, low-osmolar nonionic dye, which is now only slightly more expensive, can be used. The literature supports that nonionic dye produces less left ventricular dysfunction, bradycardia, and hypotension, as well as less nausea and emesis. Thus, it is useful in cases of suspected left main stenosis, severe left ventricular dysfunction, and severe aortic stenosis. Other indications for nonionic dye are severe renal dysfunction and a reported allergy to contrast dye. However, no reduction in acute renal failure or anaphylactoid reaction has been conclusively demonstrated with the use of nonionic dye. There is evidence that nonionic contrast is more thrombogenic than ionic contrast. Therefore, it should be used carefully in patients with acute coronary syndromes. Whenever nonionic contrast is used, 5 IU of heparin per cubic centimeter of contrast should be added.

2. Dye allergy

- a. **Premedication.** If a patient reports an allergy to contrast dye or a history of prior anaphylactoid reaction, it is customary to premedicate with steroids and antihistamines. Protocols vary widely. Common regimens include 50 mg of oral prednisone administered 13, 7, and 1 hour (q6h) prior to the procedure along with diphenhydramine 50 mg IV or orally 1 hour prior to the procedure. Intravenous steroids can be substituted in place of oral steroids 1 hour prior to the procedure (hydrocortisone 100 mg IV once). With a history of possible life-threatening dye allergies, it is also prudent to administer small quantities of dye (1 mL) and observe the patient for a few minutes before proceeding.
- b. **Treatment.** If a patient develops any sign of an allergic reaction, treatment should be prompt. If signs such as hives or rashes develop, treatment with diphenhydramine is usually sufficient. Hydrocortisone is also often given, though its effects may not manifest for several hours. In cases of oropharyngeal edema, bronchospasm, or hypotension, 0.3 mL of 1:1,000 epinephrine should be administered subcutaneously. With refractory symptoms, 10 µg/min of intravenous epinephrine can be administered until symptoms abate.
- c. **Latex allergy** has become increasingly recognized as a clinical entity, especially in patients who are health-care workers. True latex allergy can include urticaria, angioedema, laryngospasm, bronchospasm, and anaphylaxis. If a patient describes a possible latex allergy, allergy testing, including skin testing and rapid antigen serum testing, should be considered. Patients with latex allergy should be scheduled as the first case of the day to avoid latex dust from previous procedures. Written protocols outlining materials to be avoided should be strictly followed. A cart with latex-free items should be made available. The sheath is a source of latex exposure. Therefore, a sheathless approach involving catheter exchanges over a wire is preferred.
- d. **Sedation.** Commonly used sedatives include the benzodiazepines midazolam 1 to 2 mg IV or lorazepam 1 to 2 mg IV. Some operators use fentanyl 25 µg IV or morphine 1 to 2 mg IV for pain relief. Diphenhydramine 25 or 50 mg IV can also be used for sedation. Continuous pulse oximetry should be followed to ensure that sedation has not been excessive.
- e. **Radiation safety.** Radiation poses a threat to laboratory personnel; therefore, every effort should be made to reduce exposure. The source is scatter from the x-ray beam originating under the table. Lead aprons (with at least 0.5-mm thick lead lining) and thyroid collars are mandatory to minimize

radiation exposure. Leaded eyeglasses should also be considered. In addition, radiation badges are worn inside the lead apron and outside the thyroid collar to monitor cumulative radiation exposure. A leaded acrylic shield should be used between the patient and the operator closest to the patient. Standing further from the table also reduces radiation exposure by the inverse square of the distance. A number of additional steps can be taken to minimize radiation to both the operator and the patient. Fluoroscopy and, in particular, cine time should be minimized. The image intensifier should be positioned as close as possible to the patient to reduce radiation scatter. To decrease radiation, higher magnification should be used judiciously. “Coning down” on a region of interest with the use of collimators can also reduce the amount of radiation, as can the use of lung field collimators. Right anterior oblique (RAO) views produce less radiation scatter for the operator than left anterior oblique (LAO) views. Higher cine frame rates increase radiation exposure; use of 15 or 30 frames/s produces less radiation exposure than use of 60 frames/s. In the rare situation that a pregnant patient needs catheterization, a lead apron should be used. This precaution should also be taken for premenopausal women.

V. ACCESS SITE

A. Femoral artery. Femoral artery cannulation is the most common form of arterial access for cardiac catheterization (see Fig. 64.1). The patient is first positioned appropriately, with the knees about 12" apart. The table should allow enough movement to perform fluoroscopy of the groin. Anatomic landmarks are then identified. The inguinal ligament is located. Then the femoral pulse is palpated approximately 2 cm (finger breadths) below the inguinal ligament; this marks the site of arterial access.

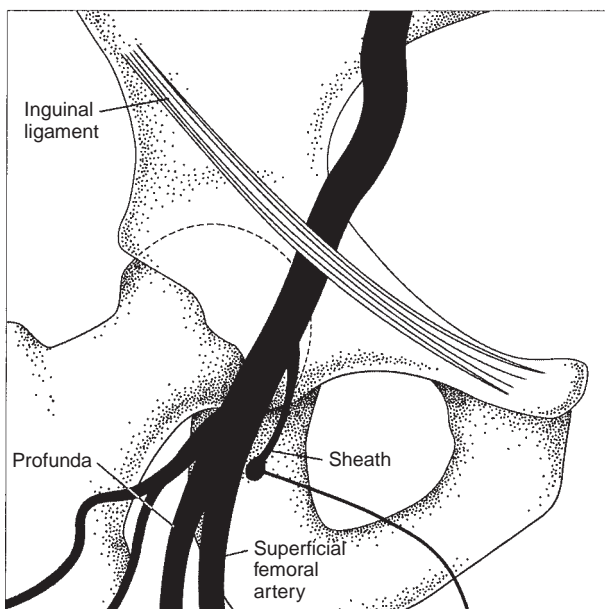


FIGURE 64.1 Landmarks for right femoral artery puncture.

Alternatively, fluoroscopy can be used to locate the femoral head. The entry point on the skin is located over the inferior border of the femoral head. Care must be taken not to enter the artery above the inguinal ligament, as this increases the chance of retroperitoneal bleeding. Arterial entry that is too low must also be avoided, as this can lead to pseudoaneurysm or arteriovenous fistula formation. Once the site of entry has been identified (and marked, if so desired), the area is cleaned with povidone iodine (Betadine) and surgically draped. Local anesthesia is given slowly (it hurts less when delivered slowly) while the clinician monitors the HR and watches for signs of a vagal reaction (nausea, lightheadedness, and yawning). The usual choice is procaine 1%. A subcutaneous wheal is raised with about 3 mL using a 25G needle. Next, an additional 6 to 10 mL is delivered to the deeper tissues with a 22G needle. In patients who are allergic to ester-type anesthetics, lidocaine 2% can be used. Once the site is anesthetized, an 18G Cook needle is inserted into the artery. Upon nearing the artery, a side-to-side motion of the needle indicates a position either medial or lateral to the artery. Up-and-down motion indicates correct positioning. In addition, when the needle is above the artery, it transmits the arterial pulsation to the fingertips. Once brisk arterial blood return is established, a 0.035" J-tipped 45-cm guidewire is inserted, the needle is withdrawn, and an arterial sheath with a dilator is placed over the wire. Then the wire and dilator are removed. The sheath is then flushed with saline. A 5F or 6F sheath is generally used for diagnostic catheterizations in the United States, though 4F sheaths are often used in Europe. An 8F sheath is used for acute cases or planned interventions. A 5F sheath is preferred over larger sheaths for patients with peripheral vascular disease.

- B. Brachial and radial approach.** In certain patients, it may be desirable to perform the catheterization by a brachial or radial route, for which specialized equipment is available. Percutaneous brachial or radial access is similar to the femoral approach described above. In addition, a surgical cut-down was historically performed to enter the brachial arteries under direct visualization, though surgical cut-downs are rarely performed in the modern era. For a left brachial approach, Judkins catheters are adequate. For a right brachial approach, Amplatz or multipurpose catheters are used, although it may be difficult to engage a left internal mammary artery (LIMA) graft from the right arm; a specially designed brachial internal mammary artery catheter is available for the latter purpose. In rare circumstances, an axillary approach can be used, though the rate of neurovascular complications is higher.

Increasingly, operators now use the **radial approach** as the default approach. The radial approach has been associated with fewer bleeding complications when compared with the femoral approach and does not require a long period of immobilization of the patient afterward. It is thus preferred by patients. Radiation exposure data have been conflicting and can be influenced by multiple factors including the familiarity of the operator with the radial approach. To obtain vascular access from the radial site, the Allen test should be performed prior to radial artery catheterization. The patient's arm is abducted at a 70° angle and the wrist is hyperextended. The site is prepped and draped in a manner similar to the femoral and brachial access sites. Local anesthetic is injected. The radial site should be roughly 1 cm above the styloid process. Either an 18G needle or a micropuncture needle (22G) is inserted at 30° to 45° into the radial artery. A sheath is advanced in the same manner as described above using the Seldinger technique. Local infusions of nitroglycerin and/or verapamil can be injected to decrease radial artery spasm. Heparin 3,000 to 5,000 IU should be considered to avoid sheath thrombosis. Once access is obtained, a similar process of advancing a catheter over a guidewire is performed as in other access sites. Diagnostic and interventional procedures can be performed via the radial artery using traditional catheters as well as a number of newer catheters designed specifically for radial access such as the Jacky catheter or the Tiger catheter.

- C. Special situations.** In patients with prosthetic femoral grafts, it is preferable to use a dilator first before placing the sheath to prevent the sheath from kinking as it passes through the graft. This technique is also useful in obese patients. If a synthetic graft is old, fluoroscopy can be performed to determine if the graft is heavily calcified—a sign that it may not seal well after sheath removal. In patients with tortuous or diseased vessels, a Wholey wire or Terumo guidewire can be used to get catheters up the aorta. If marked iliac tortuosity is present and causes inability to torque catheters, a long sheath can be used to straighten out the iliac vessel. At times, a stiffer wire (such as an Amplatz wire) can provide better support to advance catheters. In patients with an AAA for whom a femoral approach is chosen, exchange wires should be used for every change of catheter. Use of a softer wire (such as a Wholey wire) can prove less traumatic to the vessel, as can use of a JR 4 to direct the guidewire.
- D. Catheters.** The catheters commonly used for coronary angiography include the Judkins and the Amplatz systems. For the left coronary artery (LCA), the size of the Judkins left (JL) catheters ranges from JL 3.5 to JL 6. The Amplatz left (AL) catheters used commonly range in size from AL I to AL III (Fig. 64.2 shows the shapes of the JL and AL catheters). Similarly for the right coronary artery (RCA), the Judkins right (JR) catheters range in size from JR 3.5 to JR 6. The Amplatz right (AR) catheters commonly used range from AR I to AR III. In addition, there is also an AR-modified catheter (Fig. 64.3 shows the shapes of the JR and AR coronary catheters commonly used). Other catheters used include the multipurpose catheters (multipurpose A1, A2, B1, and B2 catheters), which can be used for cannulating the left and right coronary arteries and bypass grafts. For coronary bypass grafts, the right or the left coronary bypass catheters may be used. The internal mammary artery may be cannulated using either the internal mammary or the internal mammary special catheters (see Fig. 64.4).

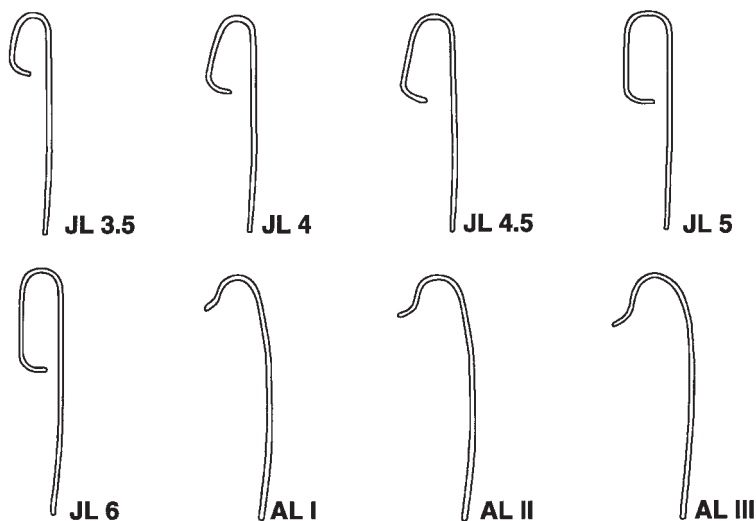


FIGURE 64.2 Catheters used for cannulating the left coronary artery. JL, Judkins left; AL, Amplatz left.

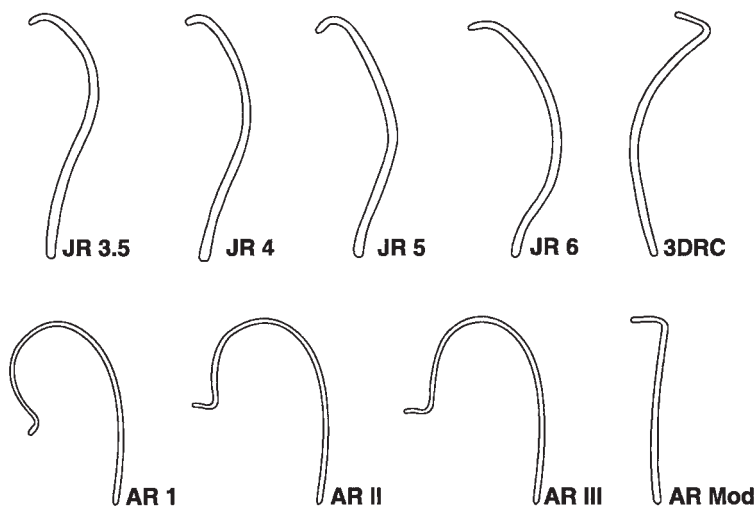


FIGURE 64.3 Catheters used for cannulating the right coronary artery. JR, Judkins right; AR, Amplatz right; 3DRC, no torque right coronary catheter; Mod, modified.

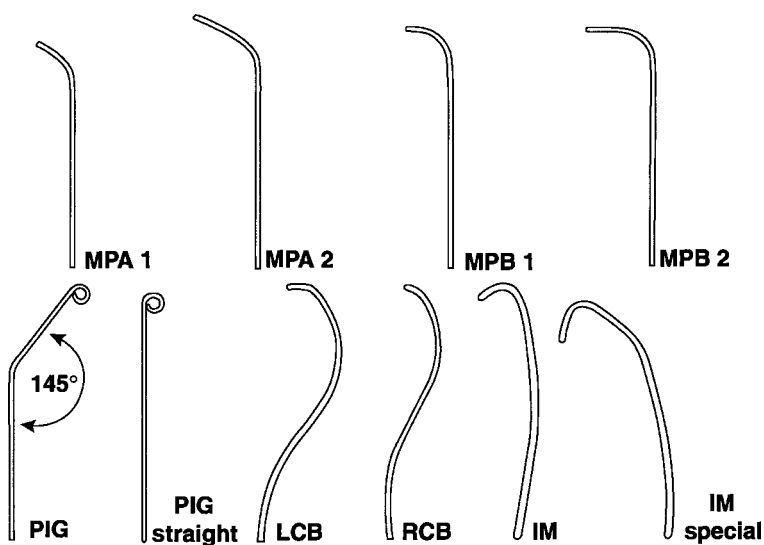


FIGURE 64.4 Other catheters used for cardiac catheterization. MP, multipurpose; PIG, pigtail; LCB, left coronary bypass catheter; RCB, right coronary bypass catheter; IM, internal mammary.

VI. TECHNIQUE

A. Engaging the vessel

1. **Left coronary artery.** Catheters are flushed with heparinized saline and passed through the sheath over a J-tipped guidewire. Using fluoroscopic guidance in the LAO projection, the left main coronary artery is cannulated, typically with a JL 4 (see Fig. 64.2). The catheter tip should be coaxial to the left main coronary artery, meaning that its tip should not be touching the upper wall of the left main coronary artery. In a small person, a JL 3.5 (see Fig. 64.2) catheter can be used. In a larger person or a person with a dilated aorta, a JL 5 or even a JL 6 (see Fig. 64.2) can be used. If the catheter does not engage the left main ostium easily, a slight clockwise or, more often, a counterclockwise rotation of the catheter hub may help. With the JL catheters, unless the aorta is dilated and provides no hinge point for the JL catheter, counterclockwise rotation moves the catheter tip anteriorly and clockwise rotation moves it posteriorly.

Care should be taken to prevent the catheter from too deeply engaging ("deep-seating") the left main coronary artery. The pressure waveform must be observed for **damping** (a decrease in the systolic pressure) or **ventricularization** (when the waveform looks like a ventricular pressure tracing), both of which indicate a need to pull the catheter back and also raise the possibility of significant left main CAD. An adequate amount of dye reflux should be seen, unless ostial disease is present. If significant left main CAD is suspected, a cusp view (with the catheter placed in the left sinus of Valsalva) can be taken. Injection of contrast should be gentle and pressure gradually increased ("ramping"). Enough contrast should be injected to opacify the entire coronary artery and ensure reflux into the aorta (usually about 8 mL for the LCA). Injection force should be forceful enough to prevent "streaming," the inadequate opacification of coronary arteries that can create the illusion of stenoses. Care should be taken to inspect the injection syringe for air bubbles before each injection and to hold the syringe upright while injecting.

2. **Right coronary artery.** Catheterization of the RCA is similar to that of the LCA, except that a JR 4 (see Fig. 64.3) is advanced into the right coronary cusp, again in the LAO projection. The RCA is usually located anteriorly in the right sinus, in a position that is lower than the LCA ostium. As the catheter is slowly pulled back 2 cm above the aortic valve, it is rotated clockwise, causing it to engage. With the JR catheter, clockwise rotation moves the catheter tip anteriorly. In addition, clockwise rotation can cause the catheter tip to dip downward. Thus, it may be necessary to apply backward traction on the catheter as it is being rotated clockwise. Sometimes, it is necessary to repeat the clockwise rotation at different levels in order to engage the right coronary ostium. If the JR 4 does not easily engage the RCA or if the pressure dampens, ostial disease, spasm, selective intubation of the conus (which arises separately 50% of the time), or anatomic variation in the direction of the proximal RCA should be suspected. A cusp view can be taken to clarify these situations. Care should be taken to avoid subselectively intubating the conus branch.

If difficulty is encountered in engaging the RCA because of the orientation of the ostium, a 3DR or a no-torque right catheter can be useful (see Fig. 64.3). Both catheters are designed to be placed above the aortic valve and pulled back without torquing maneuvers. An Amplatz or multipurpose catheter (see Figs. 64.3 and 64.4) can be useful for an upwardly angled ostium. An anterior or posterior origin can often be engaged with an Amplatz catheter. The most common cause of an incomplete LHC is a high and anterior RCA. To locate its ostium, less clockwise torque should be applied to the catheter so that it faces more anteriorly. Then the catheter can search for the ostium superior to the usual location. Less dye is needed to opacify the RCA than the LCA; overinjection can cause ventricular fibrillation. Sometimes, if a catheter is tenuously engaged, particularly in the right coronary ostium, a deep breath can dislodge it and should be avoided.

3. **Left internal mammary artery.** Catheterization of the LIMA is done either in the posteroanterior or shallow LAO projection. First, the catheter (usually a JR 4 catheter or a LIMA catheter; see Figs. 64.3 and 64.4) is positioned by pulling it back in the aorta while applying counterclockwise torque until it enters the left subclavian artery. At this point many operators will obtain an angiogram of the left subclavian artery to rule out a stenosis proximal to the LIMA and to give a hint of the angle of takeoff of the LIMA. The wire (J-tipped guidewire or Wholey wire) is then advanced into the subclavian artery. Next, the catheter is advanced over the wire into the subclavian artery, the wire is removed, and the catheter is slowly pulled back with a slight counterclockwise rotation until it engages the ostium of the LIMA. Movements around the ostium must be gentle to reduce the risk of dissection of the vessel; frequent test injections are helpful. In addition, if a 6F sheath is in place, switching to a 5F catheter will likely result in less trauma to the ostium of the LIMA. Turning the head to the left or right and pulling the arm caudally are maneuvers that can help engage the LIMA. If the ostium points downward at a sharp angle, the LIMA catheter is more likely to engage it selectively. The special LIMA catheter provides a slightly different angulation. It is best to use nonionic contrast to minimize the pain caused by ionic dye running through the arteries of the chest wall. If the ostium cannot be engaged successfully, a nonselective angiogram can be taken with the tip of the catheter as close to the ostium as possible. A blood pressure cuff should be inflated above systolic pressure in the left arm to facilitate dye movement down the LIMA.
4. **Right internal mammary artery (RIMA).** Catheterization of the RIMA is similar to that of the LIMA. The catheter (either JR 4 or LIMA; see Figs. 64.3 and 64.4) is placed in the brachiocephalic trunk by pulling it back in the aorta while applying counterclockwise rotation. The wire is advanced into the right subclavian artery. Care must be taken to avoid the right carotid artery. The wire is removed and the catheter is pulled back until it engages the ostium of the RIMA.
5. **Saphenous vein grafts (SVGs).** Catheterization of SVGs depends on the specific type of graft. The grafts are by necessity anastomosed to the anterior surface of the aorta. The orientation of SVGs from caudal to cranial is usually as follows: RCA, left anterior descending artery (LAD), diagonal branches of LAD, and marginal branches of left circumflex coronary artery (LCX). In the LAO view, grafts to the RCA usually point to the patient's right, whereas grafts to the left system are usually oriented more to the patient's left. It is the practice of some surgeons to place circular graft markers around the ostia of the vein grafts on the outer surface of the aorta. In the steep LAO projection, the catheter tip should extend beyond the plane of these markers, if the catheter is truly engaged in a vein graft. Injections into presumed vein graft stumps should be forceful to ensure that the graft is truly occluded, as opposed to poor opacification from a tenuously engaged catheter. Review of the operative note is mandatory before catheterization to know where grafts were placed. In particular, it should be noted whether any LIMA or RIMA grafts are in situ or free (attached to the aorta). A previous catheterization, if done, should be reviewed. Particular attention should be paid to the location of the grafts. The relative relationship with surgical clips should be noted, as this will save time and effort in finding grafts during the catheterization. If a graft cannot be found or a stump identified during a catheterization, an aortogram should be performed (Section VI.E).
 - a. **SVG to RCA.** Engaging this graft can be as simple as pulling back on the JR 4 as it sits in the ostium of the RCA while in the LAO projection. Often, this graft has a steep downward orientation from the aorta. In this situation, a multipurpose catheter can be useful in engaging the graft. The multipurpose catheter can enter deeply into the graft if not handled carefully. Alternatively, a right bypass catheter or a right-modified Amplatz catheter can be useful in engaging the RCA graft.

- b. **SVG to LAD.** The graft to the LAD is most easily engaged in the RAO view. To engage this graft, it is necessary to withdraw the catheter from the SVG to the RCA by pulling back. If the catheter does not fall into place, clockwise rotation of the JR 4 at an area cranial to the SVG to RCA graft ostium will locate the LAD graft. It may be necessary to move the catheter up and down along the anterior surface of the aorta several times. Left bypass, left Amplatz, and multipurpose catheters are all alternative catheters that can be used. A similar clockwise rotation to move the catheter tip along the anterior aortic surface is necessary.
- c. **SVG to LCX.** To engage this graft, it is necessary to withdraw the catheter from the SVG to the LAD by pulling back, while remaining in the RAO projection. If the catheter does not fall into place, clockwise rotation of the JR 4 at an area cranial to the SVG to LAD graft ostium will locate the LCX graft. The technique is otherwise similar to that for engaging the graft to the LAD.

B. Imaging the vessels

1. **Normal coronary anatomy.** The left main coronary artery originates from the left coronary cusp. It usually bifurcates into an LAD and an LCX, although it sometimes trifurcates to include a ramus intermedius. The LAD courses along the anterior interventricular groove, supplying numerous septal perforators to the septum and a variable number of diagonal branches to the anterolateral wall of the left ventricle, and usually continues to the apex. The LCX courses along the left atrioventricular (AV) groove, providing a variable number of marginal branches to supply the lateral wall. In some institutions, the first marginal branch is called the high lateral branch of the circumflex, with subsequent branches called lateral or posterolateral branches depending on their destination. The LCX continues in the AV groove for a variable distance. In patients in whom the LCX is dominant (see subsequent text), the LCX reaches the posterior interventricular groove and gives rise to a posterior descending artery (PDA) branch.

The RCA originates from the right coronary cusp and courses along the right AV groove, providing atrial branches (to the right atrium) and marginal branches (to the right ventricle). A conus branch originates as the first branch from the proximal RCA to supply the right ventricular outflow tract; about half of the time, this branch has an ostium that is separate from the RCA ostium. It is usually unnecessary to visualize a separate conus branch, unless collaterals to the LAD are suspected. The RCA gives off a branch to the sinus node about 60% of the time (otherwise a left atrial branch of the LCX serves this function). The first major branch the distal RCA gives off is the PDA, in a right dominant system. **Dominance** refers to which artery gives off a PDA and supplies the posterior part of the heart. In about 85% of patients, this will be the RCA; in 7% the RCA and LCX will be codominant; and in another 8% the LCX will be dominant. The PDA courses along the inferior interventricular groove, providing septal perforators to supply the inferior septum. After giving off a PDA, the RCA continues as a posterolateral segment supplying a variable number of posterior ventricular branches. From this posterolateral segment, the RCA usually (90% of the time) provides a branch to supply the AV node.

2. **Basic principles.** Several views of the coronary arteries are required to prevent excessive overlap of vessel segments and to delineate the severity of stenoses. A general principle that is useful is that in an RAO view the spine is on the left of the screen, conversely, in an LAO view the spine is on the right of the screen. Cranial views bring the silhouette of the diaphragm into the field of view. The diagonal and obtuse marginal branches tend to move in synchrony, because they supply the lateral aspect of the heart, whereas the LAD is located on the anterior portion of the heart. The AV continuation of the LCX lies in the AV groove, and (in patients with sinus rhythm) it has an “atrial kick” to it. This type of atrial kick can also be seen in atrial branches from either the LCX or the RCA. In the RAO view, a diagonal branch, and not the LAD itself, usually lies on the heart border. In the LAO view, the LAD runs along the border of the heart silhouette, not the

diagonal branches. Caudal angulation tends to move posterior vessels (such as the posterolateral branches of the RCA or the obtuse marginal branches of the LCX) inferiorly. Cranial angulation tends to move posterior vessels superiorly.

Patients should be instructed to take in a deep breath and hold it before most views for the purpose of moving the diaphragm out of the way. The RAO cranial view can be done at end of expiration to facilitate the splaying out of the diagonals from the LAD or at end of inspiration to view the proximal LCX. The LAO caudal can be done at end of expiration to visualize the left main and ostial LAD or at end of inspiration to view the LCX. Panning motion should be smooth and slow. It is best to wait for two to three systolic cycles and focus on proximal vessels before panning down the length of the artery of interest. It is important to pan to look for collaterals.

3. Different views (see Figs. 64.5 to 64.11)

a. Left coronary artery. There is wide variation in the sequence of views obtained. Many operators start with a posteroanterior view and focus on the left main coronary artery, sometimes with a coned-down view to improve resolution. The problem with a pure posteroanterior view is that there is significant overlap with the spine. Therefore, a little bit of RAO angulation ("shallow RAO") can be used to get the coronaries off the spine. A steeper amount of RAO provides greater separation of the LAD from the LCX. A slight amount of caudal angulation can be used to decrease the foreshortening of the proximal circumflex in the straight RAO view and to place the diagonals below the LAD. Therefore, a **20° RAO, 20° caudal** is often the first view, displaying the entire left coronary system. This view also provides

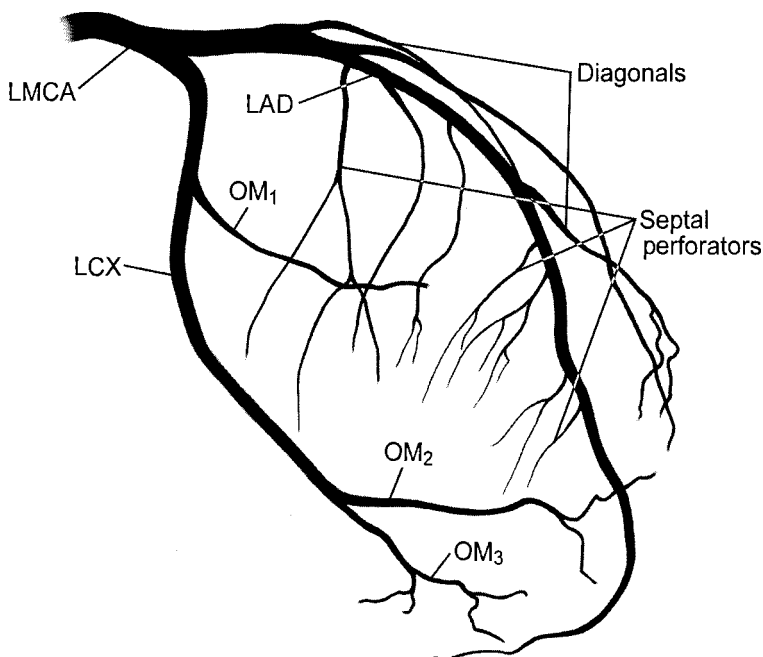


FIGURE 64.5 Posteroanterior view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery; OM₁, obtuse marginal branch 1; OM₂, obtuse marginal branch 2; OM₃, obtuse marginal branch 3.

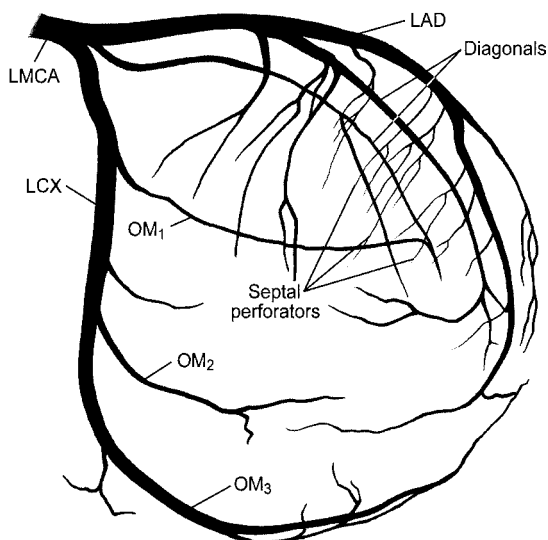


FIGURE 64.6 Right anterior oblique caudal view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery; OM₁, obtuse marginal branch 1; OM₂, obtuse marginal branch 2; OM₃, obtuse marginal branch 3.

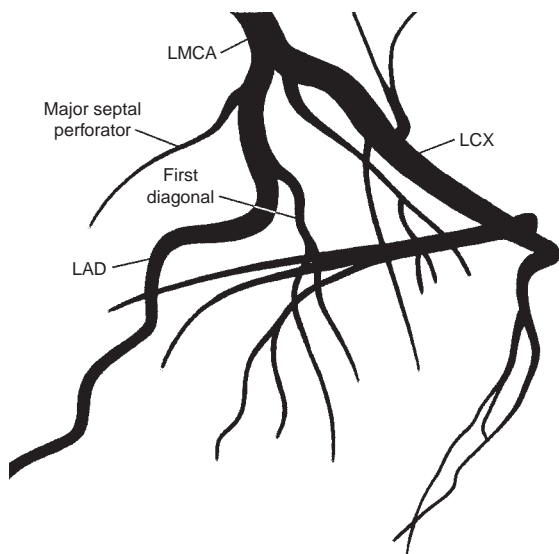


FIGURE 64.7 Left anterior oblique cranial view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery.

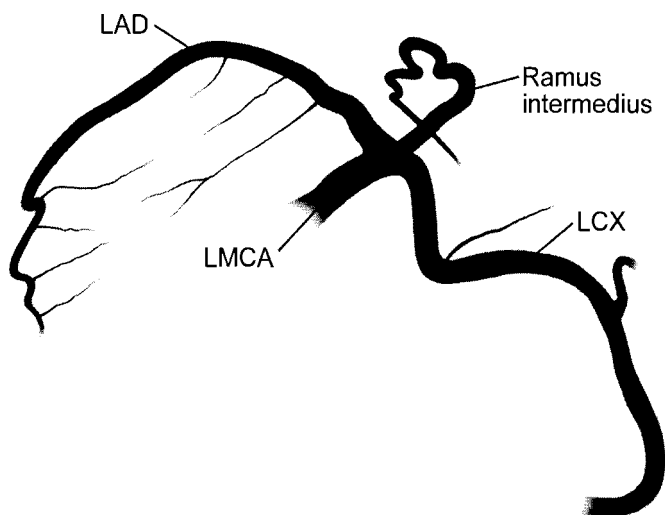


FIGURE 64.8 Left anterior oblique caudal view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery.

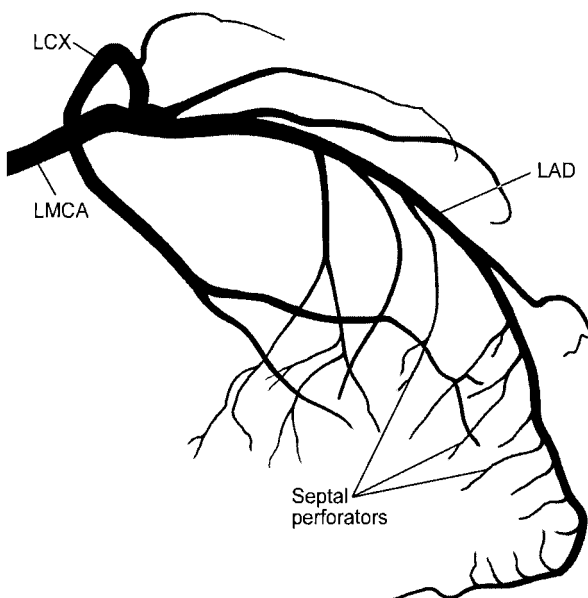


FIGURE 64.9 Right anterior oblique cranial view of left coronary artery. LMCA, left main coronary artery; LCX, left circumflex coronary artery; LAD, left anterior descending artery.

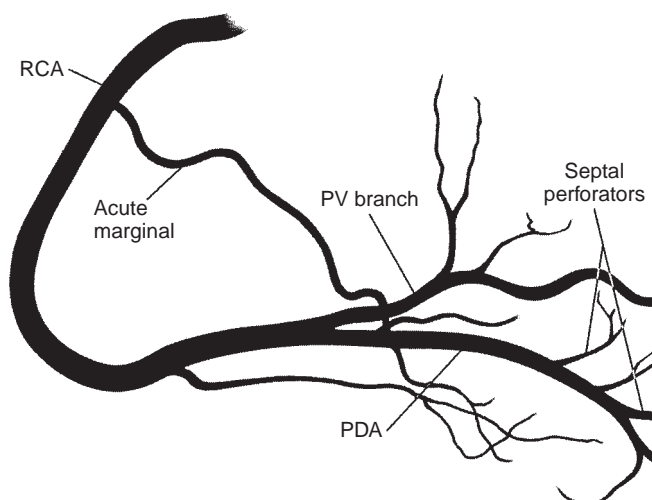


FIGURE 64.10 Left anterior oblique view of right coronary artery. RCA, right coronary artery; PV branch, posteroventricular branch; PDA, posterior descending artery.

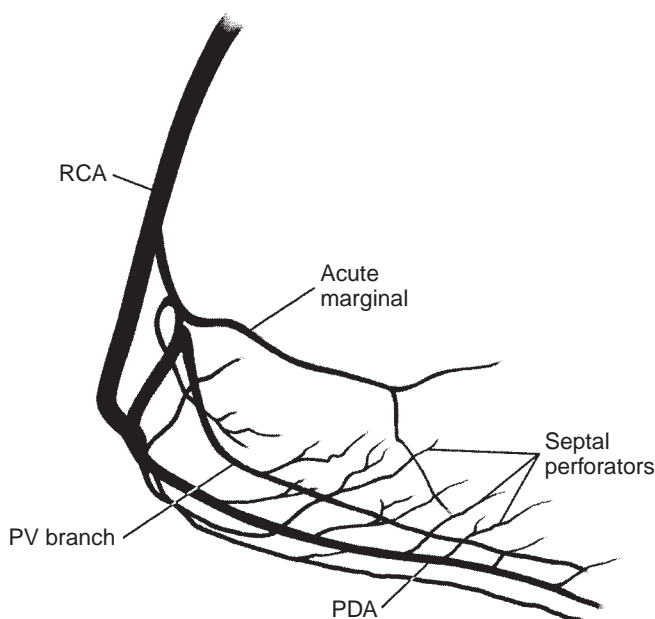


FIGURE 64.11 Right anterior oblique view of right coronary artery. RCA, right coronary artery; PV branch, posteroventricular branch; PDA, posterior descending artery.

a good view of the proximal LCX and of the origin of a ramus intermedius branch, if present. The contour collimator (called the wedge or the shield) should be moved to the upper right of the screen. A **30° RAO, 25° cranial** view can be used to separate the diagonals from the LAD, placing them above the LAD. The wedge should be placed in the upper right of the screen. A posterior–anterior view (PA) with **40° cranial** angulation can be useful in viewing the mid and distal portions of the LAD. The **45° LAO, 30° cranial** view is good for separating the LAD from its diagonal branches, especially for vertically oriented hearts. There should be enough LAO angulation to get the LAD off the spine. This view can also be good for a left-sided PDA branch. Steeper degrees of LAO further separate the LAD from the LCX and can get the LCX off the spine, but they can also cause the origins of the diagonals to overlap the LAD and cause the distal LAD to overlap the diaphragm. The **45° LAO, 30° caudal** (“spider” view) is useful for looking at the left main coronary artery and the proximal origin of the LCX. The proximal LAD is also seen but is foreshortened, unless the heart is horizontal in orientation. There must be enough LAO to get the cardiac silhouette off the spine. There is usually no need for a wedge, as it further increases the haziness of this view. Minimal to no panning is required. The **lateral** view provides delineation of the mid-LAD. In addition, the distal LAD does not overlap the diaphragm and the LCX is off the spine. The patient’s hands should be placed behind the head for the lateral view. The shield should be placed above the course of the LAD. Panning involves dropping the table height and moving the table cranially. The **PA with 30° caudal** angulation provides a good view of the LCX.

- b. **Right coronary artery.** The RCA is usually viewed in LAO and RAO views. The **30° RAO** view provides a good view of the proximal and mid-RCA and also of the PDA, which is laid out lengthwise. Cranial angulation can help separate the PDA from the distal vessel. The **40° LAO** view provides a good view of the proximal and mid-RCA, and if cranial angulation is added, a good view of the posterolateral arteries. The **PA with 30° cranial** can provide a useful view of the origins of the PDA and posterolateral branches. The lateral view of the RCA can provide a good view of the mid-RCA. In the RAO view, the right atrium and ventricle are separated by the RCA in the AV groove. Thus, atrial branches will be directed toward the atrium and marginal branches will be directed toward the ventricle.
- c. **Bypass grafts.** An LAO view and an RAO view are required to visualize the body of the graft. Additional views are dictated by the grafted vessel. A particularly useful view for the LIMA–LAD anastomosis is the lateral view; cranial LAO and cranial RAO views can also be useful. The graft to the diagonal can be visualized in the cranial LAO and cranial RAO views. The graft to the marginal branch can be seen in the RAO and lateral views. The graft to the distal RCA can be visualized in the cranial LAO and lateral views.
4. **Congenital coronary artery anomalies.** Coronary artery anomalies should be suspected if there is an absent coronary artery and a large area of myocardium that appears nonperfused. The most common anomaly is an absent left main coronary artery trunk, in which the LAD and LCX have separate ostia (incidence 0.47%). If the LAD is first cannulated, the LCX can be engaged with a clockwise rotation; sometimes one size larger catheter (JL 5) is needed. Likewise, if the LCX is first cannulated, counterclockwise rotation, perhaps with a smaller-sized catheter (JL 3.5), is needed to engage the LAD. Other common anomalies in order of importance are the LCX originating from the right sinus of Valsalva (0.45%) and the RCA originating from the ascending aorta above the sinus of Valsalva (0.18%). The RCA originating from the left sinus of Valsalva is the next most common anomaly, originating superior and anterior to the left main (0.13%).

The origin of the left main artery from the right sinus is even less common (0.02%), but it can result in sudden death if the left main artery passes between the aorta and the pulmonary artery (extremely rare). The left main artery can also pass into the ventricular septum (most common), anterior to the pulmonary artery or posterior to the aorta. The 30° RAO view can help define the relationship between the coronary artery and the great vessels. If the course is septal, septal perforators can be seen originating from the left main.

The other coronary anomalies occur much less frequently. The Amplatz (left or right, depending on the cusp of origin) and multipurpose catheters are especially useful in cannulating anomalous coronary arteries.

Although not truly a congenital anomaly, every angiographer should be aware of **myocardial bridging**. This is an apparent narrowing of a coronary artery (usually the mid-LAD) that is present only during systole. There have been reports of bridging involving the diagonal branches of the LAD, the marginal branches of the LCX, and the distal RCA. Because the majority of coronary blood flow occurs during diastole, myocardial bridges are rarely pathologic, but there have been patients treated with CABG and, more recently, stenting. Nitroglycerin, by dilating epicardial vessels, can make bridging seem even more pronounced. A phenomenon similar to bridging can occur in hypertrophic obstructive cardiomyopathy, in which septal perforators from the LAD can become obliterated during systole.

5. **Quantification of coronary stenosis.** It is important to always obtain at least two perpendicular views of each coronary artery lesion. A single view, or even multiple views, can miss an eccentric lesion. Severity of a lesion is based on percent diameter stenosis compared with a “normal” reference segment. Lesions are generally classified as severe if 70% or more are in the LAD, LCX, and RCA or 50% are in the left main artery. When measuring the size of vessels and stenoses, it is useful to note that a 6F catheter has an external diameter of 2 mm. Formal quantitative coronary angiography or use of calipers can improve the measurement of coronary artery stenoses. Quantitative coronary angiography decreases the interobserver and intraobserver variabilities of grading stenosis severity. The minimal luminal diameter in the most severe view correlates best with perfusion imaging; minimal luminal diameters < 1.2 to 1.5 mm in proximal vessels typically reduce hyperemic flow.

6. **Limitations of coronary angiography.** Sometimes the severity of a lesion is difficult to gauge based on visual angiographic estimates alone, particularly in the presence of diffuse disease. Angiography only provides an outline of the lumen, the so-called luminogram. In addition, the angiogram can underestimate the presence of atheroma because of outward remodeling of the arterial wall (the Glagov phenomenon). Furthermore, angiography can only visualize arteries > 200 μ m in diameter. The physiologic importance of 40% to 70% stenoses cannot be determined by angiography alone, and flow limitation should be demonstrated before percutaneous intervention. Techniques such as intravascular ultrasound and determining the fractional flow reserve can aid in determining whether ambiguous lesions on angiography are significant. Intravascular ultrasound provides a 360° tomographic view of the vessel lumen rather than a two-dimensional luminogram. Diagnostic applications of **intravascular ultrasound** include **imaging of angiographically indeterminate lesions, assessment of left main CAD, detection of transplant coronary vasculopathy, and identification of vulnerable plaques**. Intravascular ultrasound and optical coherence tomography can also be used during coronary interventions to help guide angioplasty, atherectomy, and stent placement (see Chapter 65, Percutaneous Coronary Intervention, for more details on these adjunct techniques of imaging).

C. Crossing the aortic valve

1. **Normal aortic valve.** The pigtail catheter is most commonly used to cross native aortic valves. Tissue valves can also be crossed, but crossing mechanical valves (e.g., St. Jude, Björk-Shiley, and Medtronic-Hall) risks catheter entrapment and is best

avoided. The catheter should be made to loop above the aortic valve. When pulled back very slowly, the catheter should give in, and it can then be rapidly advanced into the left ventricle during systole. Having the patient take a deep breath and hold it while the pigtail catheter is being unlooped can facilitate the passage of the catheter into the left ventricle. Sometimes the guidewire itself may be useful in crossing the valve, in which case the catheter is simply advanced over the guidewire into the left ventricle. A single operator can cross the aortic valve without assistance, but if two operators are present, one can move the catheter and change its orientation while the other moves the wire back and forth. The pressure in the left ventricle is recorded continuously; the catheter is pulled back into the aorta in a single motion to determine the aortic pressure, and the pullback pressure gradient can be calculated.

2. **Aortic stenosis.** In more severe cases of aortic stenosis, difficulty may be encountered in passing any catheter across the aortic valve. In this circumstance, a 0.038" straight-tipped wire can be used to cross the valve. If this method is elected, some operators recommend a 5,000 IU bolus of heparin. The timer should be started, and not more than 3 to 4 minutes should be allowed per attempt at crossing. Between each attempt the wire should be withdrawn and wiped, blood aspirated and discarded, and the catheter flushed. Special care must be taken during this maneuver to avoid perforating the aortic cusps or potentially dissecting the coronary ostia. If a 6F sheath is used, a 5F pigtail catheter often provides the correct angle for wire passage; in addition, aortic and femoral pressures can be recorded concurrently and compared with the left ventricular pressure simultaneously using two transducers. A JR 4 or AL I catheter can also provide the correct orientation for wire passage across the aortic valve. The combination of a Feldman catheter and a Rosen wire is an alternative approach to cross stenotic aortic valves. Another way to determine the pressure gradient is to use a double-lumen pigtail catheter and measure the left ventricular and aortic pressures simultaneously.

D. Left ventriculography

1. **Setting up the view.** The pigtail catheter (commonly the angled version) is positioned in the midcavity of the left ventricle. The pigtail catheter should look like a "6" in the RAO projection. If the pigtail catheter twists with each beat, this indicates that it is caught in the mitral valve apparatus and needs to be repositioned. The monitor should be observed for ectopy. Once a stable rhythm is present, ventriculography can proceed. First, the left ventricular end-diastolic pressure (LVEDP) should be measured on a 40 scale. In patients with an elevated LVEDP (> 25 mm Hg), a left ventriculogram is generally contraindicated. If the decision to proceed with the left ventriculogram is made, sublingual nitroglycerin should first be given to lower the LVEDP. With more moderate degrees of left ventricular dysfunction, nonionic dye, which is less of a myocardial depressant, can be used. Digital subtraction can be used instead of cinefluoroscopy to obtain the left ventriculogram. This allows a smaller amount of contrast to be used. With digital subtraction, the view must be carefully centered because panning is not possible. **The left ventriculogram is best avoided in patients with critical aortic stenosis, significant left main artery disease, or severe left ventricular dysfunction.**
2. **Views.** The 30° RAO view is used to look at the overall left ventricular function. In particular, the anterior, apical, and inferior walls can be assessed (see Fig. 64.12). Some operators routinely pan to the LIMA to assess its patency in a patient who might require CABG. The RAO view is also useful to assess mitral leaflet prolapse and MR. The LAO cranial view can also be used to assess MR, and it avoids the overlap of the aorta with the left atrium that occurs in the RAO view. **MR** can be graded on a scale of 1 to 4; 1 represents trace MR, with mild left atrial opacification that clears with one beat; 2 represents a mild to moderate degree of opacification, though less than that of the left ventricle; 3 represents moderate to severe opacification of the left atrium equal to that of the left

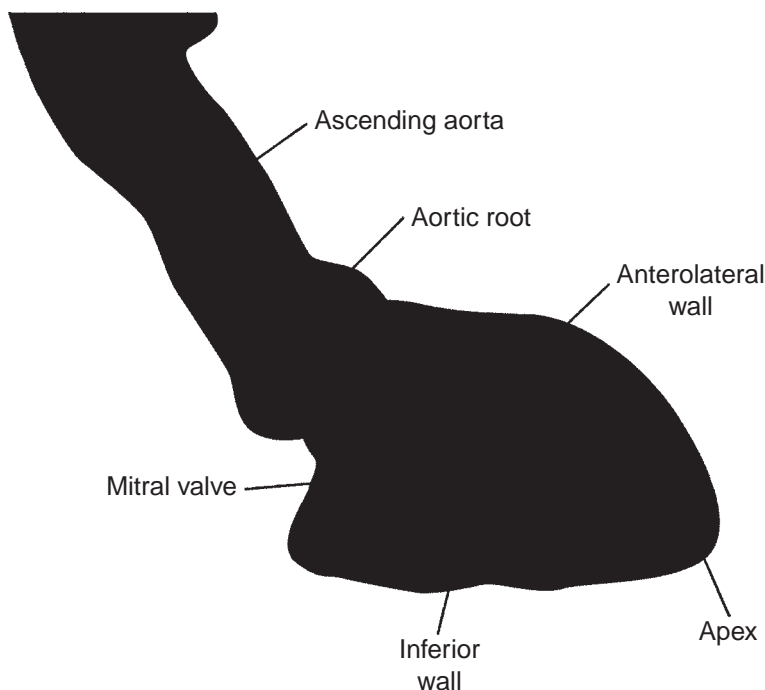


FIGURE 64.12 Thirty-degree right anterior oblique view of the left ventricle.

ventricle; and 4 represents complete opacification of the left atrium greater than that of the left ventricle. Panning toward the left atrium may be needed if MR is present. The catheter itself can cause MR if it is caught in the mitral valve apparatus or if it induces premature ventricular contractions. The correlation between angiographic and echocardiographic MR is excellent. The **60° LAO** projection allows evaluation of the septum and the posterior and lateral walls (see Fig. 64.13). Ventricular septal defects are best identified in the LAO projection with slight cranial angulation. If biplane imaging capability exists, RAO and LAO views of the left ventricle can be obtained simultaneously.

3. **Settings.** For a ventriculogram, the flow injector can be set at a rate of 10 to 15 mL/s for a total volume of about 35 to 50 mL, with a rate rise of 0.4 second (to minimize ectopy and to keep the catheter from moving abruptly) and a pressure of 600 PSI. The exact settings will vary depending on the size of the heart and the need to limit contrast.
- E. **Aortography.** Aortography is usually performed in the LAO position, with the catheter about 2 cm above the aortic leaflets. Compared with a ventriculogram, a larger volume of contrast is needed to opacify the aorta. The flow injector is set to a higher total volume than for the left ventriculogram, usually about 60 mL at a rate of 20 to 25 mL/s. No rate rise is necessary (other than to keep smaller catheters from moving), and a pressure limit of 600 PSI is used. **Aortic insufficiency** can be identified with a grading system similar to that of MR; 1 represents trace aortic insufficiency that clears from the left ventricle with each beat; 2 represents mild left ventricular opacification that takes more than one beat to clear; 3 represents moderate left ventricular opacification

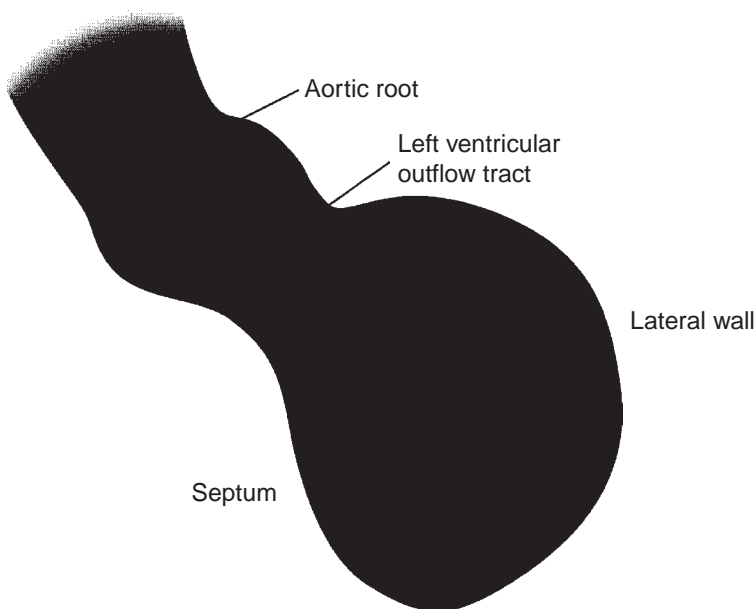


FIGURE 64.13 Sixty-degree left anterior oblique view of the left ventricle.

equal to that of the aortic root; and 4 represents complete opacification of the left ventricle greater than that of the aortic root. Diseases of the aorta such as aneurysms or dissection can also be identified. An aortogram can also aid in nonselective visualization of anomalous coronary arteries or grafts that are difficult to engage. However, the absence of filling of a bypass graft on an aortogram does not exclude its presence. The aorta must be completely opacified to ensure that grafts are seen.

An aortogram can be performed with the pigtail catheter placed in the descending aorta slightly above the level of the origins of the renal arteries (the L1 vertebral body) to rule out **renal artery stenosis**. A JR 4 can be used to obtain selective renal arteriograms by turning the tip of the catheter so that it points to either the left or the right in the posteroanterior view. The catheter is then gradually pulled back when it is in the vicinity of the renal artery ostia until it engages. Digital acquisition should be used.

Carotid angiography is sometimes necessary to confirm the degree of carotid artery stenosis seen on a noninvasive study. A variety of catheters (the Headhunter and Newton series) can be used to selectively cannulate the common carotid artery. These catheters are advanced to the aortic arch over a guidewire and pulled back to engage the artery of interest. A Newton 5 can be used to engage the right common carotid artery and a Newton 2, with its smaller curve, can be used to engage the left common carotid artery. There is a 0.5% to 1% risk of stroke with this procedure. Digital acquisition and use of nonionic contrast are mandatory.

- F. Pharmacologic testing.** In patients in whom coronary artery spasm is suspected, intravenous methylergonovine can be given to provoke spasm. Once significant angiographic stenosis has been ruled out, 0.05 mg of intravenous methylergonovine is administered. If the patient develops his or her typical chest pain or ST elevation on electrocardiographic monitoring, the coronary arteries are catheterized immediately. The electrocardiographic changes can help determine which coronary artery to cannulate

first. If there are no electrocardiographic changes or chest pain, the right coronary artery (which is statistically more likely to have spasm) and then the left coronary artery should be recatheterized 5 minutes after the methylergonovine has been administered. A positive response consists of a focal area of spasm that is relieved by intracoronary nitroglycerin (a usual dose of 100 to 200 μ g). Diffuse spasm can be physiologic, and it is also managed with nitroglycerin and verapamil (also 100 to 200 μ g). Because the half-life of methylergonovine is longer than that of sublingual nitroglycerin, it is important to realize that spasm can recur after a dose of nitroglycerin. If the initial dose of methylergonovine does not provoke a response, an additional dose of 0.2 mg can be given a few minutes after the first. Alternatively, some operators prefer giving a single dose of 0.2 mg.

Intracoronary vasodilators such as nitroglycerin are often used in the assessment of coronary anatomy. For example, if the operator is unsure if what appears to be ostial disease of a coronary artery may in fact be catheter-induced ostial spasm, an intracoronary injection of nitroglycerin and repeat angiography can help clarify. For more on the use of intracoronary vasodilator therapy (including nitroglycerin, nitroprusside, and adenosine) in the assessment and treatment of CAD, please see Chapter 65, Percutaneous Coronary Intervention.

Intravenous infusion of dobutamine can be useful in the evaluation of patients with low-flow/low-gradient aortic stenosis and left ventricular dysfunction. These patients can be a challenging population to evaluate, as it is unclear if the valve stenosis is in fact severe or moderate. The measurement of peak valve gradients and valve area at baseline and during administration of a dobutamine infusion can help clarify this question. Patients who do not have true anatomically severe aortic stenosis will exhibit an increase in valve area, with little change in the peak gradient during an increase in stroke volume caused by dobutamine infusion.

VII. POST-CATHETERIZATION CARE

A. Sheath removal. The sheath is removed once the procedure is complete. Adequate local anesthesia should be reinjected if the previously given dose has lost its efficacy. After the sheath is removed, hemostasis is generally obtained with direct manual pressure of the fingertips over the pulse, without sterile gauze to obscure the view. Pressure is held for approximately 20 minutes (about 3 minutes for each French size) until there is no bleeding. Manual pressure remains an important technique due to low cost, good safety profile (complication rate < 0.23%), short learning curve, and ability to be employed despite femoral artery dissection, significant peripheral vascular disease, or a low stick. To shorten the time of manual pressure, hemostatic pads can be used. These products are impregnated with a procoagulant mixture that causes local vasoconstriction and potentiates clot formation. Care must be taken to intermittently allow adequate blood flow to the distal extremity. It is, therefore, best if one can directly visualize the extremity to assess its color. If both arterial and venous sheaths are present, it is best to remove the venous sheath first and then obtain hemostasis before removing the arterial sheath. In patients with severe aortic stenosis or significant left main CAD, laboratory personnel should be prepared to rapidly manage a vagal episode, which can be life threatening in these situations. Adequate administration of anesthesia before removal of the sheath decreases the chance of a vagal reaction.

Bed rest is generally required for 6 hours after a femoral sheath is removed, although some operators require 1 hour for each French size. In fact, 2 hours is a sufficient period of bed rest for 5F sheaths. Two hours of keeping the arm straight is necessary after a brachial or radial procedure. During the postprocedure observation period, it is necessary to monitor the HR, temperature, blood pressure, urine output, distal pulses, and the access site (for pain, bleeding, or hematoma). Using sandbags over the groin site is discouraged. Before discharge, it is best to have the patient ambulate under observation. Specific discharge instructions should include the possibility of late access site bleeding and the need to hold pressure and call for emergency help.

Intravenous fluids are often given after a cardiac catheterization. The osmotic load of the contrast dye can cause a large diuresis. Intravenous fluids (e.g., normal saline at 100 mL/h for several hours) can prevent volume depletion. Care should be taken in patients with a history of congestive HF, in whom liberal intravenous fluids could contribute to pulmonary edema.

B. Compression/closure devices. The use of femoral artery closure devices offers the advantages of improved patient comfort, potentially lower complication rates, early sheath removal, and early hospital discharge, and anticoagulation may be continued without interruption in some patients. The currently available products include compression devices such as the FemoStop (RADI Medical Systems) and the C clamp, biosealants (Duett, vascular solutions), collagen plugs (Vasoseal; Datascope), vascular sandwiches (Angioseal; Daig), and percutaneous sutures (Perclose, Prostar, and Techstar; Abbott).

1. The **FemoStop** is a pneumatic compression device that can be used for holding pressure in cases of prolonged bleeding. The **C clamp** is a mechanical clamp that can also be used for holding prolonged pressure. If either of these devices is employed, direct supervision of the patient is required.
2. **Biosealant** (Duett) devices consist of a procoagulant mixture of collagen and thrombin that is deployed in the tissues surrounding the arterial puncture site through a balloon catheter. This device allows early ambulation. The disadvantages of this device include delayed reuse of the arteriotomy site (repeat arterial puncture cannot be performed for about 3 months) and possibility of infection due to the foreign material introduced; it can also be cumbersome to deploy, and in rare cases, inadvertent deployment of the procoagulant mixture into the femoral artery may result in arterial occlusion requiring surgical intervention.
3. The **Angioseal** (St. Jude/Kensey Nash) hemostatic puncture closure device can be used to obtain hemostasis in an uncomplicated femoral procedure if an 8F or a smaller sheath was used. Before deploying the Angioseal, it is advisable to obtain an angiogram of the femoral artery to ensure that the entry site of sheath is above the bifurcation of the common femoral artery. It is available in 6F and 8F sizes. A biodegradable collagen plug is deployed at the femoral artery puncture site using a guidewire and special sheath. No manual pressure is required, and ambulation can begin after 1 hour. The Angioseal device is user friendly due to its ease of deployment and general reliability. The disadvantage of this device is the introduction of foreign material that could be a potential source of infection, and repeat arterial puncture cannot be performed at the same site for about 45 to 60 days.
4. The **Vasoseal** (Datascope) is a collagen plug that is placed over the femoral artery puncture site. It comes in several sizes; to determine the appropriate size, it is necessary to place a depth marker on the needle during the initial arterial puncture. Ambulation can begin 1 hour after the placement.
5. The **Perclose** (Abbott) is a percutaneous vascular suture device that allows immediate ambulation (of course, after the effects of any sedation given during the procedure have worn off). Before its use, a 35°-RAO view of the right femoral artery should be taken to ensure that the sheath has been placed above the femoral artery bifurcation. The device is currently available in 6F, 8F, and 10F sizes. Other improved devices are likely to be available in the near future.
6. The **StarClose Vascular Closure System** (Abbott) is a percutaneous vascular closure device that employs a nitinol clip. Before its use, a view of the right femoral artery should be taken to ensure that the sheath has been placed above the femoral artery bifurcation. The device is delivered through a sheath onto the arteriotomy site, and the clip takes hold of the tissue in a circular manner and closes off the arteriotomy site.

VIII. COMPLICATIONS

A. Death. There is a 0.1% risk of death from LHC. This risk is substantially higher in patients undergoing urgent catheterization for acute coronary syndromes. In addition,

patients with left main CAD, severe aortic stenosis, or severe left ventricular dysfunction are known to be patient subgroups with a particularly increased risk. Advanced age increases the risk of death.

- B. Myocardial infarction.** There is a 0.05% risk of MI from LHC. MI can result from coronary dissection, disruption of a preexisting atheromatous plaque, and a large air embolus or a thrombus. Patients with acute coronary syndromes have a higher risk of MI.
- C. Stroke.** Stroke occurs in 0.05% of catheterizations. There is a risk of stroke from an inadvertent air embolus or thrombus. The presence of aortic atheroma is a risk factor for embolic complications. Dislodgement of atheromatous debris in the aorta can lead to a stroke. This risk can be minimized by the use of 260-cm exchange wires for catheter changes in patients with known severe aortic disease.
- D. Coronary artery dissection.** Engagement of the coronary arteries can rarely cause dissection. It is most often due to the injection of contrast through a catheter that is not coaxial to the coronary artery, causing rupture of a preexisting plaque, or placement of the catheter too deeply into the coronary artery (so-called deep throating). Particular caution should be used with Amplatz catheters. In cases of left main coronary artery dissection, a stent can be placed emergently and the patient can be placed on peripheral cardiopulmonary support until the surgical team can be mobilized.
- E. Coronary artery spasm.** Engagement of the coronary arteries, in particular the RCA, can cause spasm. This is best treated with withdrawal of the catheter. Subsequent reengagement and administration of intracoronary nitroglycerin (100 to 200 µg) may also be necessary for more rapid resolution of spasm.
- F. Renal failure.** Contrast dye can precipitate renal failure in any patient, although certain patients (those with elevated creatinine, diabetes, proteinuria, or dehydration) are at higher risk. Adequate prehydration with normal saline can reduce this risk. In some cases (especially in diabetics with renal insufficiency and those with renal artery stenoses), patients may need to be admitted to the hospital for hydration with 0.45% saline for several hours before the LHC to minimize risk of contrast-induced nephrotoxicity. The use of the antioxidant *N*-acetylcysteine (600 mg orally twice daily) before and after exposure to radioccontrast along with 0.45% saline prevented the decrease in renal function in patients with chronic renal insufficiency exposed to nonionic low-osmolality contrast agent. This study, however, enrolled only 83 patients. Other studies have examined the role of sodium bicarbonate infusions in preventing contrast-induced nephropathy. Several small studies have shown benefit with the use of sodium bicarbonate infusions (3 ampules of sodium bicarbonate in 1 L normal saline, infused at 3 mL/kg/h for 1 hour before procedure and 1 mL/kg/h during the procedure and for 6 hours following) or sodium bicarbonate plus *N*-acetylcysteine in preventing contrast-induced renal function. In a study of 129 patients with serum creatinine concentrations of 1.5 to 3.5 mg/dL who underwent coronary or aortofemoral angiography, use of the iso-osmolar, dimeric, nonionic contrast medium iodixanol was associated with decreased risk of nephropathy compared with the low-osmolar, nonionic, monomeric contrast medium iohexol.

The best way to minimize contrast-induced renal failure is to limit the amount of dye used. Using < 30 mL of contrast dye dramatically reduces the incidence of renal failure in even the highest risk patients. Biplane cineangiography can maximize the amount of information obtained with each view.
- G. Emergency CABG.** There is a risk of needing emergency CABG as a complication of the catheterization (e.g., dissection of the left main coronary artery). There is also the possibility of identification of critical disease, such as severe left main CAD, that may prompt emergency CABG as the most expedient treatment.
- H. Arrhythmias.** A risk of ventricular fibrillation (0.5%) exists with catheterization. This rhythm is treated with electrical defibrillation. In particular, overinjection of contrast into the RCA can cause ventricular fibrillation. Contrast dye (less so nonionic dye) can cause transient bradycardia, best dealt with by having the patient cough and by minimizing the amount of dye injected with each angiographic procedure.

- I. **Heart failure.** The osmotic load of contrast dye can put a patient with diminished cardiac or renal function into overt pulmonary edema. In patients with severe cardiac or renal disease, injection of contrast should be limited, and the use of nonionic, low-osmolar dye should be considered.
- J. **Vagal reaction.** If a patient develops hypotension and/or bradycardia, a vagal reaction should be considered. It is a common occurrence when local anesthetic is being administered or when the sheath is being removed. Atropine 1 mg IV should be available and given in these situations. Adequate anesthesia can help prevent such reactions. In a patient with severe aortic stenosis or left main CAD, a vagal reaction can start a downward spiral that leads to death. Levophed (about 10 µg) should always be available and used immediately in such cases of hypotension.
- K. **Vascular**
 1. **Femoral.** Pseudoaneurysms, arteriovenous fistulas, arterial thrombosis, and peripheral emboli are possible vascular complications. Careful technique can minimize these events. In particular, paying attention to puncture location and obtaining adequate hemostasis after sheath removal are the best ways to decrease vascular complications. For example, smaller sheaths (5F) are preferred in patients with significant peripheral vascular disease. Frequent aspiration and discarding of blood from the arterial sheath, followed by gentle flushing, is useful. If an attempted cannulation is unsuccessful but an arterial puncture has been made, the needle should be withdrawn and adequate manual pressure held (about 5 minutes). If a venous puncture has been made inadvertently, the needle should be removed and pressure held (for about 3 minutes). Proceeding directly to arterial puncture without removing the needle and holding pressure increases the chance of arteriovenous fistula formation. If a venous puncture is planned, it should be made at a site lower than the arterial puncture site. Bruits should be auscultated both before and after the procedure. A new bruit may indicate a vascular complication. **Ultrasound** is an essential part of managing groin complications. If there is a large pseudoaneurysm present, surgery may be required after a trial of ultrasound-guided compression. Percutaneous injection of thrombin into the pseudoaneurysm has proven to be a more effective alternative to compression. Small pseudoaneurysms (< 2 cm) tend to close spontaneously but should be followed by serial ultrasound examinations. An arteriovenous fistula that does not close spontaneously in 2 to 4 weeks may require surgical repair.
 2. **Brachial/radial.** When using an upper extremity approach, blood pressure should first be checked in both arms. If there is a difference in blood pressure between the arms, peripheral vascular disease should be suspected and the side with the higher blood pressure should be used. For a radial approach, an Allen test must be performed to assess the patency of collateral ulnar circulation. The rate of vascular complications such as thrombosis is higher with the upper extremity approach than with the femoral approach.
- L. **Bleeding.** Access site bleeding can be significant. If there is a great deal of oozing around the sheath, it can be exchanged for a sheath 1F size larger. Adequate manual pressure is usually sufficient to stop bleeding after sheath removal. It is a typical practice to check the activated clotting time in patients who had been on heparin before the procedure and only proceed with sheath removal if the clotting time is below 160 seconds. Some institutions use protamine (1 mg/100 IU heparin) to reverse heparinization, but this exposes the patient to the potential for allergic reactions to protamine (namely, hypotension). Even more concerning is **retroperitoneal bleeding**. If a patient complains of severe back pain after a catheterization, this should be considered. An unexpected drop in hemoglobin after a catheterization should also raise this possibility. Obese patients, in particular, can have a major bleed without obvious external signs. Noncontrast computed tomography scan of the abdomen and pelvis can diagnose a retroperitoneal bleed, but it is important to assess the patient's clinical stability before sending them to such a study. Patients who have developed a documented retroperitoneal hematoma or are suspected of having this complication are monitored

closely in an intensive care unit, often with continuous blood pressure assessment using an arterial line and receive aggressive volume resuscitation with fluids and blood products until self-resolution with reversal of anticoagulation or definite treatment.

- M. Infection.** There is a risk of infection, as with any invasive procedure. This risk can be minimized with proper attention to sterile technique. There is usually no need for prophylactic antibiotics. However, some operators do give antibiotics after use of a percutaneous vascular suture device in patients who are at elevated risk for infection, such as obese or diabetic patients. Endocarditis prophylaxis for patients with valvular heart disease or prosthetic valves is unnecessary.
- N. Neuropathy.** There is a slight risk of damage to the femoral nerve from inadvertent puncture. Femoral hematoma (or retroperitoneal bleeding) can also cause compromise of the femoral nerve. Function usually improves with time, but complete recovery can take several months.
- O. Allergy.** As discussed above, contrast dye can cause adverse reactions, ranging from hives to anaphylaxis. Severe anaphylactoid reactions to contrast dye occur in about 0.1% of cases. Local anesthetics can also cause problems due to specific allergies to the amide or ester component or to the preservative. A variety of agents are available. Procaine (an ester agent), lidocaine (an amide agent), and bupivacaine (a preservative-free amide agent) are alternative agents.

ACKNOWLEDGMENTS: *The author thanks Drs. Saif Anwaruddin, Niranjan Seshadri, and Deepak L. Bhatt for their contributions to previous editions of this chapter.*

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Percutaneous Coronary Intervention

I. INTRODUCTION

- A. Coronary atherosclerosis may result in a flow-limiting stenosis that leads to myocardial ischemia and/or myocardial infarction (MI). Andreas Gruentzig first managed these lesions percutaneously on September 16, 1977, when he advanced a fixed-wire, distensible balloon across a stenosis in the mid-left anterior descending (LAD) artery and briefly inflated it to 6 atm (90 psi). This procedure was termed percutaneous transluminal coronary angioplasty (PTCA). With the advent of stents and other therapeutic coronary devices, these procedures are now more broadly termed percutaneous coronary intervention (PCI). It is estimated that more than 1 million PCI procedures are completed in the United States and approximately 2 million worldwide annually.
- B. The field of interventional cardiology continues to rapidly evolve, as a result of many important advances in equipment, strategies, and adjunctive medication. These advances have been paralleled by a concomitant improvement in the safety and efficacy profile of PCI. The assimilation of a large body of basic and clinical research encompassing all areas of interventional cardiology continues to redefine the standard of care paradigm.

II. PCI INDICATIONS

- A. **Central tenet.** Although there is no substitute for sound clinical judgment, PCI is generally reserved for patients in whom there is an objective demonstration of myocardial ischemia or symptoms as well as angiographic demonstration of obstructive coronary disease. PCI may not be indicated for asymptomatic or mildly symptomatic patients who have only a small area of viable or jeopardized myocardium, have no objective evidence of myocardial ischemia, have other life-limiting disease processes, or have lesions that have a low likelihood of success (Tables 65.1 and 65.2).
- B. **ST-segment elevation myocardial infarction (STEMI).** **Primary PCI should be the preferred treatment strategy for patients presenting with STEMI to a facility experienced with and capable of performing PCI.** Randomized trials have demonstrated that clinical outcomes are improved when such patients are emergently transferred to centers able to perform primary PCI as opposed to therapy with thrombolytics—despite a significant delay (mean time of 44 minutes) in time to therapy due to transport. This seems especially true of patients presenting 3 to 12 hours after symptom onset, where the superiority of primary PCI becomes clearly evident. In those presenting within 3 hours of symptom onset, mortality data would suggest that either therapy is equally efficacious in appropriate candidates. **For a more thorough discussion of the management of STEMI, please refer to Chapter 1.**
- C. **Non-ST-segment elevation acute coronary syndrome (NSTEMI).** Unstable angina and non-ST-segment elevation myocardial infarction (NSTEMI) are considered part of the spectrum of NSTEMI. Given that individual patients presenting

TABLE 65.1 Standard Prepercutaneous Coronary Intervention Evaluation**History**

- Symptoms (angina, dyspnea, paroxysmal nocturnal dyspnea, syncope)
- Previous MI
- Previous cardiac interventions (PCI, CABG)
- Comorbidities (diabetes mellitus, hyperlipidemia, hypertension, etc.)

Medications (glucophage, statins, aspirin, thienopyridines, etc.)

Allergies (contrast dye, latex, etc.)

Physical exam (murmurs, jugular venous pressure, pulses, bruits, edema)

Laboratory data (creatinine, potassium, hemoglobin, platelets, INR)

Other tests (ECG, echocardiogram, stress tests)

Informed consent including risks, benefits, alternatives

CABG, coronary artery bypass grafting; ECG, electrocardiogram; INR, international normalized ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

TABLE 65.2 Considerations for Every Percutaneous Coronary Intervention

Review clinical and angiographic risk factors

Develop strategy and anticipate problems

Surgical backup

Access

Anticoagulation and antiplatelet therapy

Consider diagnostic adjuncts (e.g., PA line)

Consider therapeutic mechanical adjuncts (e.g., IABP)

Guidewire

Device (e.g., angioplasty, stent)

Closure of vascular access site

Post-PCI destination (telemetry ward, CICU)

CICU, cardiac intensive care unit; IABP, intraaortic balloon pump; PA, pulmonary artery; PCI, percutaneous coronary intervention.

with unstable angina/NSTEMI are at widely varying risk for subsequent morbidity and mortality, early and aggressive risk stratification including cardiac catheterization with subsequent percutaneous or surgical revascularization (rather than non-invasive stress testing) is recommended. This recommendation is supported by a number of clinical trials comparing an early invasive to delayed conservative strategy. **For a more thorough discussion of the management of NSTEMI, please refer to Chapter 2.**

D. Chronic stable angina. It is estimated that > 85% of all PCI procedures are performed in the elective setting for chronic stable angina. While recent trials have

questioned the mortality benefit of PCI or coronary artery bypass grafting (CABG) over optimal medical therapy in stable coronary artery disease (CAD), revascularization still remains the most rapidly effective treatment strategy for patients with angina. **For a more thorough discussion of the management of stable CAD, please refer to Chapter 6.**

III. CONTRAINDICATIONS. The only absolute contraindication to PCI is significant active bleeding, given the absolute need for procedural anticoagulation and continued dual antiplatelet therapy (DAT). Relative contraindications include a bleeding diathesis, unsuitable or high-risk coronary anatomy (e.g., chronic total occlusion in the absence of ischemia or diffuse distal disease), recurrent in-stent restenosis (ISR), and a short life expectancy because of a comorbid condition.

IV. PROGNOSIS. A patient's clinical status and coronary angiogram are powerful predictors of outcome. Certain clinical and angiographic variables have repeatedly been associated with adverse events (Table 65.3).

V. ANGIOGRAPHIC/PROCEDURAL/CLINICAL SUCCESS. Angiographic success is defined as a residual stenosis < 50% with PTCA or < 20% with stenting and is achieved in 96% to 99% of patients. The definition of procedural success is angiographic success without major in-hospital complications (i.e., death, CABG, or MI). Clinical success is defined as procedural success with relief of the symptoms and signs of myocardial ischemia.

VI. COMPLICATIONS

A. The incidence of complications (death 0.5% to 1.4%, periprocedural MI [defined by creatine kinase-myocardial band, CK-MB, elevation more than three times the upper limit of normal] up to 8%, and emergency CABG surgery 0.2% to 0.3%) has consistently decreased over the past 20 years with the advent of stents, new and more effective antiplatelet therapies, improved equipment, and increasing reliance upon evidence-based strategies.

B. Abrupt closure is the most common cause of a major adverse cardiac event (MACE) and typically occurs within 6 hours of intervention. The most common cause of abrupt

TABLE 65.3 Clinical and Angiographic Predictors of Adverse Outcomes

Clinical predictors	Angiographic predictors
<ul style="list-style-type: none"> • Older age • Unstable angina • Acute MI • Cardiogenic shock • CHF • Left ventricular function • Multivessel coronary disease • Diabetes mellitus • Renal impairment • Peripheral vascular disease • Small body size 	<ul style="list-style-type: none"> • Thrombus • Bypass graft • Left main trunk • Lesion > 20 mm in length • Excessive tortuosity of proximal segment • Extremely angulated lesions > 90° • Total occlusion > 3 months old and/or bridging collaterals • Inability to protect major side branches • Degenerated vein grafts with friable lesions • Unprotected left main trunk

CHF, congestive heart failure; MI, myocardial infarction.

closure is suboptimal stent expansion or dissection followed by thrombus, spasm, and side branch occlusion. In the mid-1980s, the risk of abrupt closure approached 5%. The common use of periprocedural glycoprotein (GP) IIb/IIIa and/or direct thrombin-inhibiting anticoagulants and stent deployment has reduced this risk to < 1% in modern practice. Risk factors for abrupt closure include presentation with acute MI, poor coronary flow postintervention (i.e., less than Thrombolysis in Myocardial Ischemia [TIMI] II), complex lesion morphology (i.e., class C lesions), and suboptimal result as judged by angiography or intravascular ultrasound (IVUS) imaging.

- C. **Atheroembolism and thromboembolism** probably occur to varying degrees in all interventions, but are most frequently encountered in cases involving degenerated vein grafts, in patients presenting with acute coronary syndromes (ACSs), and in cases using directional/rotational atherectomy. Distal embolization can result in “no-reflow” (decreased coronary flow), abrupt closure, and periprocedural MI. Thromboembolism can be minimized by using aspiration catheters (e.g., Pronto, Export, Extract) or rheolytic thrombectomy (Possis AngioJet) to remove thrombus as well as routine anticoagulant and antiplatelet therapy. The prevention of atheroembolus, most often encountered during vein graft intervention, is frequently addressed with the use of a filter device (e.g., FilterWire EZ or PercuSurge GuardWire) or proximal flow occlusion device (e.g., Proxis) to trap and remove the debris before it reaches the distal vascular bed. Intracoronary administration of vasodilators such as adenosine (36 to 72 μ g repeatedly), nitroprusside (50 to 200 μ g), and verapamil (200 μ g) has been shown to prevent and manage no-reflow, but have no effect in preventing CK-MB elevation.
- D. **Coronary perforation** is typically identified using the Ellis classification: Type I: extraluminal crater without extravasation; Type II: pericardial or myocardial blush without contrast jet extravasation; Type III: extravasation through frank (> 1 mm) perforation; Type III cavity spilling: perforation into an anatomic chamber, coronary sinus, etc. Coronary perforation is estimated to occur in 0.1% to 1.14% of routine PCI cases, 0.25% to 0.70% of cases using directional atherectomy, up to 1.3% of cases using rotational atherectomy, 1.3% to 2.1% of cases using extraction atherectomy, and 1.9% to 2.0% following excimer laser angioplasty. Contrast extravasation is typically evident in the majority of cases at the time of PCI; however, up to 20% of cases can present several hours after the procedure and are frequently due to hydrophilic wire perforation of a small vessel. Treatment usually requires prolonged balloon inflation (consider a perfusion balloon) and reversal of anticoagulation. Transthoracic echocardiography should be immediately performed in the setting of clinical instability in order to evaluate for the presence of a pericardial effusion and/or tamponade, in which case urgent pericardiocentesis is required. Covered stents, coils, or surgical repair may be required for definitive management.
- E. **Vascular access site complications** remain the most common complication of PCI and occur in up to 5% of patients. The most common are blood transfusion (3%), arteriovenous fistula (< 2%), pseudoaneurysm (up to 5%), acute arterial occlusion (< 1%), and infections (< 0.1%). Shorter anticoagulation regimens, weight-adjusted heparin, use of bivalirudin, early sheath removal, vigilant monitoring of activated clotting times (ACTs), smaller sheaths, and avoidance of routine venous sheath insertion have all contributed to a reduction in complications. Stopping heparin after PCI and substituting clopidogrel for warfarin has also resulted in a reduction of bleeding and coronary complications.
- F. **Contrast-induced nephropathy** occurs in 3% to 7% of patients, and the risk increases tenfold for patients with serum creatinine > 2.0 mg/dL, especially in the presence of diabetes mellitus. Data regarding methods to prevent renal failure are not definitive, but the most proven benefit is seen with conservative contrast utilization. In addition, use of biplane imaging can significantly reduce the amount of contrast required. Numerous studies have provided mixed results on the benefits of saline infusion before catheterization, administration of *N*-acetylcysteine (NAC) 600 mg po or IV bid for 1 day before and after the day of catheterization, single bolus dose

NAC prior to contrast load, using nonionic contrast dye, and infusion of a sodium bicarbonate solution.

- G. Contrast-mediated reactions can be serious. Anaphylactoid reactions occur in 1% to 2% of patients receiving iodinated contrast. These reactions can be severe in 0.10% to 0.23% of patients. The risk of a severe reaction can be effectively decreased by using nonionic contrast, preprocedural corticosteroids (i.e., prednisone 40 to 60 mg) given the evening before and the morning of the procedure, and the use of H₁ and H₂ blockers. If a patient presents for emergent PCI (i.e., STEMI) without having undergone preprocedural steroid preparation, the emergent administration of hydrocortisone 100 mg IV and diphenhydramine 25 to 50 mg IV is reasonable and is shown to be safe in small series. In patients undergoing an elective procedure, caution is prudent and a full premedication regimen is recommended.

- H. Stent thrombosis (ST) is discussed later in Section **XI.D**.

VII. EXPERIENCED OPERATORS/CENTERS

- A. Procedural volume is an important predictor of PCI complications. **Elective PCI** should be performed in high-volume centers (> 200 interventions per year, with an ideal minimum of > 400 cases per year) by operators with an acceptable annual volume (> 75 cases per year) at institutions with fully equipped interventional laboratories, experienced support staff, and an on-site cardiovascular surgical program. **Primary PCI for STEMI** should be performed in similarly experienced/skilled centers by operators who perform > 75 elective cases per year and intervene on at least 11 cases of STEMI per year. **Elective PCI should not be** performed by low-volume operators (< 75 cases per year) in low-volume centers (< 200 cases per year), regardless of the availability of on-site cardiothoracic surgery, because of the increased risk of suboptimal outcomes. Referral to a larger regional center is recommended in this situation.
- B. In cases of STEMI, there is an inverse relationship between the number of primary angioplasty procedures performed by an operator and in-hospital mortality. The data suggest that both door-to-balloon time and in-hospital mortality are significantly lower in institutions that perform a minimum of 36 primary angioplasty procedures per year.

VIII. SURGICAL BACKUP. Emergency surgical intervention is a rare event and is required in 0.3% to 1.0% of cases of PCI, usually because of complications that cannot be addressed percutaneously or to provide urgent hemodynamic support. The most common reasons for emergency CABG surgery are dissection resulting in acute vessel closure, perforation, inability to retrieve a stent or other device, or aortic dissection. Emergency CABG after PCI has a mortality rate of 15% and periprocedural MI rate of 12%. The internal mammary artery may not be harvested, and surgery should not be delayed due to abxiximab. Perfusion balloons may temporize a life-threatening perforation or dissection, and an intraaortic balloon pump (IABP) can minimize ischemic injury and stabilize hemodynamics. Data from the Atlantic Cardiovascular Patient Outcomes Research Team (C-PORT) and Primary Angioplasty in Acute Myocardial Infarction with No Surgery On-Site (PAMI-No SOS) trials suggest that **primary PCI for STEMI** can be safely and effectively performed in centers that **do not** perform elective PCI and do not have on-site cardiac surgery capabilities if they implement a carefully developed and proven strategy capable of rapid and effective PCI (including an experienced operator with > 75 total PCIs and at least 11 primary PCIs for STEMI per year) with a predetermined transfer plan to a nearby center with on-site surgical backup.

IX. SHEATHS, GUIDES, AND WIRES

- A. Typical arterial access involves placing a 6F to 8F short sheath in the common femoral artery using the modified Seldinger technique. Using fluoroscopic guidance when entering the femoral artery above the inferior margin of the femoral head but below the pelvic rim increases the likelihood of entering the common femoral artery

at a compressible site above the common femoral artery bifurcation and below the inferior epigastric artery. The superficial/profunda femoral artery bifurcation is best seen in the ipsilateral 30° to 40° projection. The brachial and radial arteries can accommodate up to 7F and 6F sheaths, respectively. Ulnar artery and digital arch patency should be confirmed via the Allen test in case the radial artery becomes occluded (approximately 5%). Radial access improves hemostasis and earlier ambulation but increases radiation exposure, lengthens the procedure, and limits the choice of coronary equipment (6F compatible).

- B. Larger guide size (7F or 8F) provides extra support and permits the use of larger rotational atherectomy burrs and use of kissing balloons. For straightforward lesions, a 6F system is typically adequate. The XB (extra backup) and Amplatz guiding catheters provide good support; the Amplatz guide is especially effective in cases of an acutely angled left circumflex artery, anomalous left circumflex artery originating from the right sinus, very anteriorly originating right coronary artery, or a tortuous/calcified right coronary artery. The Amplatz guide catheter is also the most likely catheter to traumatize the ostial/proximal coronary artery in inexperienced hands due to its tendency to deeply engage the vessel.
- C. The coronary lesion is initially crossed with a 0.014" diameter coronary wire, which serves as a "rail" for devices such as balloons and stents. The choice of a wire depends on the wire tip's stiffness, lubriciousness, and support characteristics. Stiff tips are helpful to penetrate chronic total occlusions but increase the risk of vessel dissection or perforation. Hydrophilic wires are quite slippery and may be used to cross tortuous high-grade lesions, but can easily cause dissection or end-vessel perforation. Support wires also typically have stiffer tips and are primarily used as a supportive rail to deliver coronary equipment through tortuous vessels. Generally, most operators routinely use a "workhorse" wire (i.e., Prowater or Balance MiddleWeight) and have "favorite" stiff (e.g., Miracle Bros series), hydrophilic (e.g., Whisper and Pilot series), and support (e.g., GrandSlam and Balance HeavyWeight) wires for use in appropriate situations. Both short (approximately 180 cm) and long (approximately 300 cm) wires are available. Most operators prefer the routine use of a rapid exchange (Rx) system, which uses a monorail that permits easy exchange over a short wire, although situations that require an over-the-wire system may be better served with the use of a longer wire to avoid dislodging the wire during equipment exchanges.

X. DIAGNOSTIC ADJUNCTS

A. IVUS (anatomic)

1. An IVUS catheter generates a cross-sectional tomographic image of both the lumen and the vessel wall. This complementary imaging modality can be invaluable when repeated angiographic views fail to determine the mechanism and/or significance of a coronary lesion. IVUS has proven helpful in assessing adequacy of coronary stent deployment, mechanism of ISR (neointimal hyperplasia versus inadequate stent expansion), a coronary lesion at a location difficult to image by angiography, a suboptimal angiographic result after PCI, coronary allograft vasculopathy after cardiac transplantation, coronary calcium when considering rotational atherectomy, and plaque location/circumferential distribution to guide directional coronary atherectomy (DCA). Further, IVUS can be indispensable in assessing the appropriate vessel size, especially during ACS when factors such as thrombus and vasoconstrictive substances can lead to significant stent undersizing.
 2. IVUS provides anatomic, not physiologic, information. However, a lumen area < 4.0 mm² in the proximal LAD, left circumflex, or right coronary artery or < 6.0 to 7.0 mm² in the left main trunk suggests the presence of a hemodynamically significant lesion.
- B. **Optical coherence tomography (OCT).** Similar to IVUS, OCT images are obtained by passing the catheter over a guidewire in the coronary artery. The catheter

acquires images during an automated pullback over 5.6 cm and requires the clearance of blood in the vessel, thereby necessitating a 15 to 18 cc contrast injection with each acquisition. In comparison with IVUS, it provides much greater image resolution but a more shallow penetration. Outside of research use, OCT is finding a place in the clinical armamentarium. The superior image quality allows an evaluation of stent apposition, poststent dissection, and analysis of plaque characteristics and plaque rupture. Recently, investigators have used OCT to evaluate endothelial stent coverage, which in the future may allow a further tailoring of antiplatelet therapy at the patient-specific level. Currently, there is a paucity of clinical outcomes data using OCT, but interest in this imaging modality is gaining momentum, with supportive data likely to follow.

- C. Angioscopy (anatomic).** Angioscopy uses a balloon-tipped catheter with a fiber optic viewport at the distal tip that allows direct visualization of the lumen. Angioscopically evident thrombus has been shown to be angiographically silent in up to 50% of patients. This imaging modality is only used for research purposes.
- D. Coronary flow reserve (CFR) (physiologic)**
1. A 0.014" wire capable of measuring coronary flow velocity permits assessment of epicardial and microvascular resistance. This information is helpful in determining whether a moderate-grade coronary stenosis (i.e., 30% to 70% stenosis) is hemodynamically significant. The ratio of hyperemic to basal flow is known as the CFR and is determined by giving an intracoronary vasodilator such as adenosine (36 to 64 μg). A normal CFR is 3 to 5. A $\text{CFR} < 2.0$ is abnormal and is consistent with a flow-limiting epicardial stenosis or increased microvascular tone.
 2. The effect of the microvasculature can be eliminated by measuring the CFR in two vessels: the lesion-containing vessel and a normal-appearing vessel. This allows calculation of the relative coronary flow reserve velocity ($\text{rCFR} = \text{CFR}_{\text{target}} / \text{CFR}_{\text{reference}}$). A nonhemodynamically significant stenosis has an rCFR value of < 0.8 and is similar in prognostic value to negative stress testing. Unlike fractional flow reserve (FFR), CFR depends on hemodynamic and microcirculatory changes. In general, FFR is the preferred diagnostic modality for assessing the hemodynamic significance of a coronary lesion.
- E. FFR (physiologic).** A 0.014" wire with a pressure transducer is placed distal to a coronary stenosis and the translational gradient measured. This allows calculation of the FFR, which is the ratio of this distal coronary pressure to aortic pressure during maximal hyperemia. A vasodilator such as adenosine (IV infusion 140 $\mu\text{g}/\text{kg}/\text{min}$ or intracoronary 36 to 64 μg) is used. A coronary artery without flow-limiting coronary obstruction would have an FFR of 1.0. An FFR value of < 0.75 to 0.80 is consistent with a hemodynamically significant obstruction and positively correlates with myocardial ischemia on stress testing. Unlike CFR, the FFR reflects only the epicardial artery lesion. Prospective studies have demonstrated that an FFR-guided strategy to direct PCI of intermediate lesions results in less stents deployed, with a significant decrease in morbidity and mortality compared with an angiography-only strategy (8.4% vs. 23.9%, $p = 0.02$).
- F. Pulmonary artery catheter (physiologic).** A balloon-tipped Swan-Ganz catheter advanced to the pulmonary arteries allows measurement of right and left heart filling pressures as well as the cardiac output. This information can be helpful in patients presenting with cardiogenic shock, during high-risk PCI in the setting of severe left ventricular (LV) dysfunction, when there is a question of pericardial tamponade, or when the cause of hemodynamic deterioration is unclear.

XI. THERAPEUTIC DEVICES

- A. Percutaneous transluminal coronary angioplasty.** The coronary balloon remains the backbone of endovascular intervention, although its sole use is in decline. The initial gain in the coronary lumen achieved by balloon inflation results in localized dissection of the intima (and often the media) plus distension of the adventitia. The

dissection is covered by platelet-rich thrombus and later by new intimal layers. As a result of these inevitable dissections, the abrupt closure rate is 4% to 7%, although the use of GP IIb/IIIa inhibitors has reduced this rate. The 6-month angiographic restenosis rate of 30% to 40% is another downside to PTCA. Furthermore, the risk of cardiac morbidity, including anginal symptoms, progressively increases with subsequent episodes of ISR following balloon angioplasty. It is recommended that patients determined to have significant ISR following PTCA should be strongly considered for coronary stent implantation.

PTCA alone may still have utility in patients presenting with ACS found to have multivessel disease suitable for urgent/emergent CABG (e.g., PTCA alone rapidly restores patency to the infarct-related artery but may allow a break in the need for antiplatelet therapy, thereby allowing the patient to proceed to surgery without delay). Even in these situations, however, aspiration thrombectomy alone may be preferred if it provides reasonable flow to the infarct artery in order to avoid the risk of mechanical complications with PTCA, such as dissection or perforation, that would require stent deployment.

B. Bare-metal stents (BMSs)

1. Present-day coronary stents are flexible, laser-cut and polished, balloon-mounted, and expandable, slotted tubes composed of either stainless steel or metal composites such as cobalt–chromium. They have proven effective in treating dissections and reducing the incidence of abrupt closure, emergency CABG (< 1%), and restenosis. First implanted in 1986 and used for emergency treatment of coronary dissection after angioplasty, the early era of the intracoronary stent placement was plagued by high rates of subacute closure despite intensive anticoagulation regimens that often led to bleeding complications and prolonged hospitalization. Evolution of stent design and interventional technique led to a rapid reduction in procedural complication rates and marked improvement in the ease of stent delivery and deployment.
2. Although subacute vessel closure may still occur in up to 3% of cases following stent implantation, by providing a scaffold and reducing elastic recoil, BMSs have reduced the published rates of restenosis from > 50% following PTCA alone to 20% to 30%. **Restenosis risk is increased in patients with small reference vessel size, smaller postprocedural luminal diameter, or high degree of residual stenosis, long lesion length, diabetes, lesion location in the LAD artery, and presence of untreated edge dissection during the procedure.** Furthermore, while stents reduce the rate of restenosis and repeat revascularization as compared with PTCA alone, they have not been shown to reduce the incidence of death or MI.

C. Drug-eluting stents (DESs). The Achilles heel of BMS has been ISR. Antiproliferative agents such as sirolimus, paclitaxel, zotarolimus, and everolimus arrest cell division during the mitotic growth phase. The use of polymers to coat these agents onto a stent's surface and provide controlled, local drug delivery has dramatically reduced neointimal hyperplasia and thereby ISR. These DESs, introduced generally in 2003, were rapidly embraced and occupied almost 90% of the stent market by 2005. Concerns about ST and the need for prolonged DAT (discussed below) have since tempered their use, and DESs now account for approximately two-thirds of stents that are deployed. There are a number of DESs available, with various studies supporting their clinical use. While a thorough discussion of trial data is outside the scope of this chapter, a brief overview is summarized below.

1. **Cypher (Cordis, NJ) sirolimus-eluting stent (SES).** The Cypher DES makes use of the BxVelocity stainless steel platform. The pivotal Randomized Study with the Sirolimus-Coated Bx Velocity (RAVEL) trial randomized 238 patients with simple lesions to SES versus a standard BMS. At 1 year, the angiographic restenosis rate (> 50%) was 0% in the SES group and 26.6% in the BMS group. Five-year follow-up of the US-approved SIRIUS trial of patients with complex coronary disease revealed durable reductions in target lesion revascularization

(TLR) compared with BMS (9.6% vs. 24.7%), with negligible differences in death and MI. A number of trials and meta-analyses have highlighted the benefits of SES, and it remains in use today. Given its stainless steel platform, this stent is often used in heavily calcified lesions or those that require high radial strength. Unfortunately, Johnson & Johnson has announced plans to discontinue production.

2. **Taxus (Boston Scientific, MA) paclitaxel-eluting stent (PES).** The Taxus DES was initially supported by the Express platform and more recently by the thinner Liberté stainless steel BMS platform. The PES was developed almost simultaneously to the SES and first studied in the TAXUS I trial in a group of patients with simple lesions; at 6 months, the PES group displayed no significant angiographic restenosis. The TAXUS IV trial compared 1,314 patients with complex native vessel coronary disease randomized to either PES or BMS and demonstrated significant reduction in TLR (9.1% vs. 20.5%) with PES at 5-year follow-up, with negligible differences in death and MI.
3. **SES versus PES.** A number of studies, some of which have been randomized, have compared SES and PES in various patient groups. Most of these trials have found that SES is superior to PES. The SIRTAX trial randomly assigned 1,012 patients presenting to the catheterization laboratory to either SES or PES and demonstrated a significant reduction (10.8% vs. 6.2%) in the rate of MACE, primarily due to reduction in the rate of TLR observed in the SES group. Similarly, in a meta-analysis of almost 9,000 patients, SES was associated with less TLR (hazard ratio [HR] 0.74) and ST (HR 0.66) than PES, with no significant difference in death or MI, at 2 years of follow-up. There is a suggestion that PES performs better in patients with diabetes, although comparisons of SES and PES even in this subgroup yield lower rates of TLR with SES use.
4. **Endeavor, Resolute, and Resolute Integrity (Medtronic) zotarolimus-eluting stents (ZES).** The Endeavor DES elutes zotarolimus from a cobalt-chromium Driver stent platform. The ENDEAVOR series of trials (I to IV) have demonstrated the effectiveness of ZES in comparison with BMS, SES, and PES. Five-year follow-up of the patients randomized in ENDEAVOR II showed a significantly lower rate of TLR for ZES versus BMS (7.5% vs. 16.3%) and equivalent rates of very late ST (0.2% vs. 0.3%). The ENDEAVOR III trial was a small study of patients randomized to ZES ($n = 323$) or SES ($n = 113$) and showed significantly higher rates of total TLR (clinically and nonclinically driven, 9.8% vs. 3.5%) but nonsignificant differences in clinically driven TLR (6.3% vs. 3.5%, $p = 0.34$) for the ZES at 8 months. The ENDEAVOR IV investigators randomized 1,548 patients to ZES or PES and found a nonsignificant trend toward higher rates of angiographic late loss at 9 months (15.3% vs. 10.4%, $p = 0.284$) and TLR at 12 months (4.5% vs. 3.2%, $p = 0.228$) in the ZES group. The large-scale Patient Related Outcomes with Endeavor versus Cypher Stenting Trial (PROTECT) is currently underway. The Resolute stent makes use of the Driver platform with a newly designed polymer that allows a delayed release of the drug for out to 3 months. The RESOLUTE US trial revealed noninferiority of the Resolute in comparison with historical Endeavor controls at 1 year. The RESOLUTE AC trial revealed no significant differences in patient- or stent-related outcomes in comparison with the Xience V at 2 years, although one cause for concern is the trend toward greater ST with the Resolute (1.9% vs. 1.0%, $p = 0.077$). The Resolute Integrity stent, available only in Europe at this time, elutes zotarolimus from Medtronic's Integrity stent platform and prides itself on improved deliverability; studies are currently underway.
5. **Xience V (Abbott Vascular, CA) and Promus (Boston Scientific, MA) everolimus-eluting stent (EES).** Sold as Xience V and Promus, the EES is based on the cobalt-chromium MultiLink Vision stent platform. The SPIRIT series of trials (I to V) have demonstrated the efficacy of the Xience V EES in comparison with

the Taxus PES. The large-scale SPIRIT IV trial was powered to assess superiority of EES over PES. Recently reported 2-year follow-up revealed significantly reduced rates of target lesion failure (TLF; cardiac death, target vessel MI, ischemia-driven TLR) (6.9% vs. 9.9%), ischemia-driven TLR (4.5% vs. 6.9%), MI (2.5% vs. 3.9%), and ST (0.4% vs. 1.2%) for EES. Notably, in the diabetic subgroup at 1 year, there was no appreciable difference in TLF (6.4% vs. 6.9%). The SPIRIT V trial of EES versus PES in diabetic patients, however, suggests a benefit of EES in this group of patients (in-stent late loss at 9 months 0.19 vs. 0.39 mm, $p < 0.01$; TLF at 12 months 11.2% vs. 12.5%, $p = 0.71$; and ST 0% vs. 1.9%). Notably, though, this was a small trial (EES $n = 218$, PES $n = 106$).

6. **Large vessels.** Retrospective subgroup analysis had suggested that large vessel DES (SES and PES) provided no significant reduction in TLR compared with BMS but did result in increased rates of ST. To address this question prospectively, the BASKET-PROVE investigators investigated patients to the use of BMS, SES, or EES in lesions requiring stents 3.0 to 4.0 mm in diameter. They found statistically similar rates of death/MI with both DES and BMS, but a decrease in target vessel revascularization (TVR) with either type of DES compared with BMS at 2 years (~3.5% vs. ~9.0%). Furthermore, definite or probable ST was not significantly different between the SES, EES, and BMS groups. These data suggest that while the rate of BMS ISR in large vessels is lower than that in smaller vessels, the benefit of DES persists to further lower the rate of restenosis without a concomitant increase in the risk of ST (as long as DAT can be continued).
- D. **Stent thrombosis** is defined as early (< 30 days), late (30 days to 1 year), and very late (> 1 year). It may be the result of stent-, procedure-, patient-, and antiplatelet therapy-related factors, and minimizing the risk of ST requires a conscious consideration of each of these issues. Compared with thrombosis of native coronary arteries, ST is associated with a higher thrombus burden and less frequent procedural success, all of which results in a much higher rate of death, recurrent MI, and recurrent ST.
 1. **Stent-related factors.** Following BMS implantation, the vascular endothelium typically grows over the stent struts in 2 to 4 weeks, thereby eliminating contact between the stent and circulating platelets with a concomitant reduction in thrombotic risk. In contrast, **reendothelialization following DES implantation is significantly retarded** because of the antiproliferative effect of the coating polymer, thereby allowing for strut/platelet contact up to several years post-PCI (similar to the historical use of brachytherapy). In meta-analyses of large trials, the **overall incidence of ST is similar in both BMSs and DESs (0.5% to 1.0% per year)**. However, **prolonged DAT is necessary in patients with DES** due to delayed endothelialization and is therefore associated with a higher risk of very late ST (approximately 0.5% per year) in patients who discontinue DAT than in patients with BMS. It is for this reason that BMS is a favored option in patients requiring PCI before major surgery or those that possess a significant contraindication to long-term antiplatelet therapy. In appropriately selected patients, however, DES is favored for its established benefits with respect to ISR and reduced need for repeat intervention.
 2. **Procedure-related factors.** **Incomplete stent apposition to plaque/vessel wall, inadequate stent expansion (i.e., stent undersizing to the vessel), and stent-edge dissection** all increase the risk of ST. While angiography may indicate all of the above problems, stent sizing is routinely underestimated by the angiogram alone. Further interrogation of the vessel using IVUS or OCT (discussed in Sections X.A and X.B, respectively) may be necessary to optimize the chances of success and minimize the risk of ST. It is **recommended that stents be expanded to 80% of the minimal reference vessel area**. Additional risk factors for ST include long lesion length, small artery diameter, and complex lesion morphology (i.e., bifurcation stenting and chronic total occlusion).

3. **Patient-related factors.** Comorbid risk factors not only are important in assessing the relative benefit of DES but also increase the risk of ST. For instance, patients with **diabetes, impaired LV function, and renal disease** not only derive greater benefit from the antirestenotic properties of DES but also present a greater risk of ST. **Premature cessation of DAT** (due to nonadherence, need for surgery, bleeding complications, or financial considerations) as well as poor clopidogrel response (seen in up to 15% of patients) also increase the risk of ST, especially in patients treated with DES.
 4. **Duration of antiplatelet therapy.** In patients with ACS, the use of 12 months of DAT is recommended for its established benefit in reducing MACE over aspirin alone. With respect to stent safety alone, however, use of 4 to 6 weeks of clopidogrel is sufficient to allow endothelialization of the BMS. For DES, numerous authors have demonstrated that cessation of DAT is a significant predictor of ST, and moreover that DES is associated with a greater risk of very late ST compared with BMS after cessation of DAT. Unfortunately, registry and small randomized trial have not proven an overall clinical benefit to prolonged DAT, although some studies have demonstrated a reduction in very late ST. Large randomized trials are currently underway to investigate the clinical conundrum of DAT duration after DES implantation. The ACC/AHA guidelines therefore recommend a minimum duration of DAT of 12 months (class I), with a consideration of DAT for > 15 months in patients with DES (class IIb).
 5. Although DESs have dramatically reduced the incidence of ISR and MACE, especially in patients with diabetes and complex coronary lesions, a mounting body of evidence suggests an increased risk of late and very late thrombosis following the discontinuation of antiplatelet therapies. Therefore, **the decision to use BMS or DES in any given patient requires a thorough evaluation** of factors that may predispose the patient to premature discontinuation of DAT (which would favor BMS). In our laboratory, the use of BMS and DES is roughly equivalent.
- E. **Covered stents.** Covered stents use a material such as polytetrafluoroethylene (PTFE), which covers the stent struts and seals off the vessel wall from the stent lumen. The Jomed covered stent has PTFE sandwiched between two Jostents. This covered stent is approved for use after coronary perforation by the Food and Drug Administration (FDA), but requires reporting of their use in this situation as a sentinel event. FDA approval can also be obtained on a case-by-case basis in patients with coronary aneurysm.
- F. **Cutting balloon atherectomy**
1. These balloons were initially developed to create a “controlled dissection.” A cutting balloon has three to four longitudinally mounted, razor-sharp atherotomes. These atherotomes cut into both plaque and vessel wall and allow vessel dilatation at a lower balloon pressure. Success in the treatment of balloon-resistant lesions led to FDA approval in 1995. Although randomized data have shown no difference between cutting balloon angioplasty and PTCA, many operators will use this device in lesions with high elastic recoil (i.e., ostial or bifurcation lesions) before DES. The AngioSculpt device consists of a balloon surrounded by a nitinol cage that prevents balloon slippage and scores the plaque. An alternative to these specialized balloons is to place a second guidewire as a “buddy” in the coronary artery, which serves as a makeshift cutting device at the lesion during balloon inflation over the first wire.
 2. Cutting balloons have also found a niche in the treatment of ISR. Regular balloons often slip when inflated across these rubbery lesions. The Restenosis Reduction by Cutting Balloon angioplasty Evaluation III (REDUCE III) trial randomized 521 patients to cutting balloon or PTCA before stenting (with angiographic or IVUS guidance) and demonstrated a significantly lower rate of angiographic

restenosis in the cutting balloon before stenting group, primarily with IVUS guidance. The “buddy wire” technique may also be useful to increase friction and minimize balloon slippage in the treatment of ISR. It is important to use a second wire that does not have a hydrophilic coating in order to maximize effectiveness.

3. Care must be taken not to oversize cutting balloons, because perforation can occur. Placing these balloons through stent struts or down tortuous vessels can result in atherotome entrapment, as can a perforated balloon. These balloons should only be inflated to 6 to 10 atm in order to decrease the likelihood of balloon rupture.

G. Rotational atherectomy

1. Rotational atherectomy uses a 160,000 rpm, diamond-coated burr (i.e., drill bit) that is advanced over a 0.009" wire to the coronary lesion. The process generates microparticulate debris that embolize and may attenuate the coronary microcirculation, inducing transient myocardial stunning, periprocedural MI, and LV dysfunction in the region of the target vessel. Therefore, although limited clinical data suggest that rotational atherectomy can be safely performed in patients with depressed LV function in the hands of an experienced operator, it is not recommended.
2. Compared with plain balloon angioplasty, rotational atherectomy increases the chance of procedural success but has not been shown to reduce the risk of restenosis or MACEs in de novo or restenotic lesions. Although the use of rotational atherectomy has declined, it is recommended before stenting in patients with severely calcified lesions, undilatable lesions, chronic total occlusions, and bifurcation lesions to help ensure proper stent expansion and apposition in balloon-resistant lesions.
3. Familiarity with the device is essential. Sluggish coronary flow can occur, requiring a vasodilator such as verapamil, nitroprusside, or adenosine. Perforation occurs in approximately 1% of patients, typically when significant tortuosity forces the burr to the outside edge of a curve. Prophylactic pacing or aminophylline is frequently required if rotational atherectomy is performed in the vessel supplying the atrioventricular (AV) node. Rotational atherectomy is typically contraindicated in patients with thrombus, dissection, or severely reduced LV systolic dysfunction. GP IIb/IIIa inhibitors decrease the risk of CK-MB elevation.

H. Directional coronary atherectomy

1. John Simpson developed DCA in the 1980s in response to the high rate of balloon angioplasty complications. DCA uses a sharp blade that repeatedly shaves off eccentric plaque and requires an IVUS to ensure adequate debulking. This revascularization technique is effective in treating fibrotic, noncalcified, ostial, bifurcation, branch ostial, or bulky eccentric lesions in large proximal vessels (> 3 mm) and requires an experienced operator for safe and effective use.

Despite multiple randomized prospective trials, optimal DCA has never been shown to have lower rates of TVR when compared with plain balloon angioplasty or stenting. As a result, DCA has little role in present-day interventional cardiology, although some cardiologists continue to use it for debulking bifurcation lesions and other eccentric, noncalcified, nonthrombotic lesions.

I. Excimer laser

1. The excimer (*excited* and *dimer*) laser catheter (excimer laser coronary atherectomy, ELCA) tip is brought into contact with the target lesion. It creates ultraviolet light (308 nm) at a rate of 25 to 40 pulses/s from a high-energy, metastable, dimeric molecule of xenon and chloride. This provides 45 mJ/mm², which can ablate 0.5 mm of tissue per second, and reduces the target tissue to gas and subcellular debris. The size of the lumen created is equivalent to that of the catheter (0.9 mm diameter).
2. The ELCA was approved by the FDA in 1992 for total occlusions, moderately calcified stenoses, balloon crossing/dilatation failures, ostial lesions, bypass grafts, and long diffuse disease. It is contraindicated in angulated lesions, coronary dissection, thrombotic lesions, and severely calcified lesions. However, long-term clinical data

have failed to demonstrate a significant restenosis benefit, and routine use increases the complication rate in comparison with plain balloon angioplasty. Therefore, the ACC/AHA PCI guidelines do not suggest use of ELCA as a primary strategy for revascularization and is used quite infrequently in the present day.

J. Thrombectomy

1. **Aspiration thrombectomy.** The use of a catheter to aspirate thrombus from the infarct artery is intuitively attractive and carries a class IIa indication in the ACC/AHA guideline management of STEMI. The Thrombus Aspiration During Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS) randomized 1,071 patients with STEMI to PCI with or without preparatory thrombus aspiration (TA) using the Export catheter. The primary end point of myocardial blush grade after intervention was higher with TA, along with less persistent ST-segment elevation, more ST-segment elevation resolution, and fewer pathological Q waves, along with a trend toward less death at 30 days ($p = 0.07$). Although clinical end points were not statistically different at 30 days, 1-year follow-up revealed significant reductions in all-cause mortality (4.7% vs. 7.6%, $p = 0.04$), cardiac death (3.6% vs. 6.7%, $p = 0.02$), and reinfarction (2.2% vs. 4.3%, $p = 0.05$) favoring TA. Similarly, a recent meta-analysis by Bavry and colleagues revealed a substantially lower mortality in patients assigned to receive aspiration thrombectomy (2.7% vs. 4.4%, $p = 0.018$) prior to PCI in STEMI. Currently, the most widely used aspiration catheters include the Pronto LP, Pronto V4, Export, and Extract (from smallest to largest lumen size; all these are compatible with a 6F system except the Extract which requires 7F).
2. **Rheolytic thrombectomy.** The Possis AngioJet is the dominant rheolytic thrombectomy device. The device is a 5F double-lumen, flexible catheter that contains a hypotube through which six high-speed saline jets create a low-pressure area at the tip (approximately -760 mm Hg), which serve to macerate and aspirate the thrombus back into the catheter lumen in accordance with the Venturi-Bernoulli principle. This catheter has proven to be successful in thrombotic vein grafts, for which it received FDA approval in 1998. Temporary prophylactic pacing is recommended when treating vessels supplying the inferior wall, because of temporary AV block. Temporary ST-segment elevation is frequent. Perforation can occur in vessels < 2.0 mm in diameter due to the high-pressure saline injection. Although small studies using the AngioJet in the setting of ACS have been encouraging, prospective randomized data demonstrating a clinical benefit have been lacking. The AngioJet Rheolytic Thrombectomy in Patients Undergoing Primary Angioplasty for Acute Myocardial Infarction (AiMI) trial randomized patients with acute MI to AngioJet thrombectomy followed by PCI or PCI alone and concluded that mortality rates (4.6% vs. 0.8%, $p < 0.02$), infarct size ($12.5 \pm 12.1\%$ vs. $9.8 \pm 10.9\%$, $p = 0.02$), and MACE rates (6.7% vs. 1.7%, $p < 0.01$) were considerably **higher** in those undergoing thrombectomy. While not used in the routine care of patients, the AngioJet still holds a place in the interventional armamentarium for patients with overwhelming clot burden that is not adequately addressed by aggressive aspiration thrombectomy alone.

K. PercuSurge GuardWire

1. Atheromatous embolization is a frequent and dreaded complication of degenerated saphenous vein graft (SVG) intervention. The first distal emboli protection device approved by the FDA was the PercuSurge GuardWire and Export catheter. The PercuSurge GuardWire is a 0.014" hypotube (i.e., hollow tube) with a balloon mounted on the distal end near the fixed floppy wire. The deflated balloon is steered across the SVG lesion and inflated in a distal portion of the graft. This results in cessation of blood flow in the SVG. Angioplasty and stenting are then performed, followed by removal of the column of blood with the Export catheter and then deflation of the occlusive balloon.

2. In the Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial, the use of the PercuSurge GuardWire resulted in the recovery of atheromatous debris (83 to 204 μm) in 93% of cases and a 42% reduction in MACE (i.e., death or MI). There was also a lower incidence of periprocedural slow flow.
3. Randomized data have failed to demonstrate the benefit of using the PercuSurge GuardWire in the setting of STEMI. The Enhanced Myocardial Efficacy and Removal by Aspiration of Liberated Debris (EMERALD) trial found no benefit to using the PercuSurge GuardWire in regard to angiographically assessed myocardial reperfusion, ST-segment elevation resolution, or infarct size at 30 days.
- L. **Filters.** Collapsible microporous polyurethane net attached to a nitinol ring anchored distally to a 0.014" guidewire that can be advanced across high-risk SVG or carotid stenoses and then deployed downstream of the lesion. When deployed, these porous devices appear as a windsock or umbrella and allow blood to flow through while filtering any debris larger than 80 to 100 μm . Advantages are ease of use and avoidance of prolonged ischemia. Potential disadvantages are incomplete sealing, passage of smaller particles through the filter pores, overloading of the device, and spillage during device retrieval. The FilterWire EX Randomized Evaluation (FIRE) trial prospectively randomized 650 patients undergoing PCI of diseased SVGs to either the EPI FilterWire EX or the PercuSurge GuardWire embolic protection device and revealed equal efficacy of both types of devices in regard to the primary end point of death, periprocedural MI, or TLR at 30 days. This trial led to FDA approval of the FilterWire EX for use in degenerated SVGs.

XII. SVG INTERVENTIONS

- A. Saphenous vein bypass grafts are frequently used in CABG surgery. However, 7% occlude the first week, 15% to 20% occlude the first year, and by the tenth year 50% of SVGs are occluded and 25% are severely degenerated. Redo CABG is high-risk surgery with high rates of morbidity and mortality that approach 7% to 10% nationally. At the Cleveland Clinic, the rate is 1.8%. A patient with a patent internal mammary artery graft to the LAD artery makes redo surgery less appealing. Patients with no arterial conduit, multiple failed SVGs, multivessel disease, and depressed LV systolic function are ideal candidates for redo surgery.
- B. Early postoperative ischemia within the first 30 days usually reflects graft failure (often secondary to thrombosis) or incomplete revascularization, and urgent coronary angiography is indicated. Emergency PCI of the graft, even across suture lines, has been safely performed within days of surgery. Intracoronary thrombolysis should be used with caution. Mechanical thrombectomy is a safer choice. Given that SVG flow is pressure dependent, IABP use should be strongly considered in patients that present with hypotension or depressed LV function.
- C. Recurrent ischemia 1 to 12 months after CABG surgery usually reflects perianastomotic graft stenosis. Distal anastomotic stenoses respond well to balloon inflation only. Midshaft vein graft stenoses are usually due to intimal hyperplasia.
- D. Recurrent ischemia > 1 year after CABG surgery usually reflects the development of atherosclerosis. SVGs have greater plaque burden than native coronary arteries, and aspirates are composed of atherosclerotic rather than thrombotic elements. This may explain the lack of benefit seen with GP IIb/IIIa inhibitors. Unprotected PCI (i.e., no PercuSurge GuardWire or filter device) results in varying degrees of atheroembolization, with 15% of patients having a CK-MB more than five times normal. Therefore, use of distal protection devices during SVG interventions is strongly encouraged when technically feasible. The use of these devices is discussed above in Section XI. In situations of poor reflow after SVG PCI, copious administration of intracoronary adenosine and/or nitroprusside is recommended, with the goal of improving microvascular flow. It should also be noted that poor reflow may be seen due to a plaque-burdened filter, which should resolve with filter retrieval.

XIII. RESTENOSIS

- A.** Restenosis is the most commonly occurring late PTCA complication and typically occurs within 6 months due primarily to vessel contracture, elastic recoil, negative vessel remodeling, and neointimal hyperplasia. **ISR is almost entirely due to neointimal hyperplasia.** Not surprisingly, focal restenosis has a better outcome and response to treatment than does diffuse restenosis. **The predictors of restenosis include diabetes, unstable angina, acute MI, prior restenosis, small vessel diameter, total occlusion, long lesion length, SVG, proximal LAD artery, higher percent stenosis after the procedure, and smaller minimal luminal diameter after the procedure.** Strategies to decrease restenosis include maximizing stent expansion (i.e., bigger is better) and minimizing the distance of arterial injury.
- B. Post-PTCA.** Balloon angioplasty alone has a 6-month restenosis rate of 32% to 40%. For restenotic lesions managed with PTCA, the restenosis rate is comparable to de novo lesions. For a third episode of restenosis, PTCA has a restenosis rate approaching 50% (not 100%). With PTCA alone, late patency is 93% after three procedures. Only 1.6% of lesions require four or more procedures. Atheroablative approaches, such as excimer laser and rotational atherectomy, have not proven superior for managing restenosis. However, stents are superior to PTCA, with a 6-month TVR rate of 10% versus 32%.
- C. In-stent restenosis.** The risk of recurrent ISR after balloon angioplasty is 10% for focal ISR, 50% for diffuse restenosis, and 80% for total stent occlusion. Atheroablative approaches, such as use of the cutting balloon and rotational atherectomy, have not proven clinically superior to PTCA.
1. ISR occurs in 17% to 32% of patients treated with BMS depending upon such variables as vessel size, lesion length, diabetes mellitus, smaller postprocedure minimal luminal diameter, higher residual percent stenosis, and vessel location. In patients who cannot receive DES but for whom ISR is an issue, consideration may be given to a short course of oral sirolimus therapy. The Oral Rapamycin in Argentina (ORAR studies I to III) investigators have found substantial reduction in TLR for BMS plus sirolimus (10 mg pre-PCI followed by 3 mg daily for 13 days) in comparison with BMS alone (8.3% vs. 38% at 1-year, $p < 0.001$) and equivalence in TLR compared with DES (8.2% vs. 7.0% at 18 months, $p = 0.84$) (1).
 2. The observed rate of ISR is significantly lower with DES. As discussed previously, 5-year follow-up from the SIRIUS trial of Cypher SES yielded a 9.1% rate of TLR, similar to the 9.6% TLR rate at 5 years in the TAXUS IV trial of PES. Follow-up data for the EES (Xience V or Promus) have been published up to 2 years in SPIRIT IV and show an ischemia-driven TLR rate of 4.5%. The Intracoronary Stenting or Angioplasty for Restenosis Reduction—Drug-Eluting Stents for In-Stent Restenosis (ISAR-DESIRE) trial compared SES and PES with balloon angioplasty in 300 patients with ISR following BMS and demonstrated a significant reduction in restenosis at 6-month follow-up in the DES groups as compared with angioplasty alone (8% vs. 33%). A comparison of EES and PES revealed a significant improvement in recurrent TLR with EES (1% vs. 11.5%, $p = 0.0193$) at 1 year, but similar rates of MI, death, and ST. Atheroablative approaches, such as use of the cutting balloon and rotational atherectomy, have not proven clinically superior to PTCA.
- D. Brachytherapy.** Brachytherapy damages chromosomes and prevents cell division, thereby inhibiting neointimal hyperplasia. Both beta and gamma brachytherapy catheter-based systems use closed-end lumen catheters that deliver the source and keep it out of contact with the blood, allowing reuse. Both gamma (iridium 192) and beta (phosphorus 32 and strontium 90) brachytherapy result in approximately a 50% reduction in ISR compared with balloon angioplasty alone. It is important to ensure brachytherapy delivery to all balloon-injured segments in the target vessel, or else inadequate radiation to an injured segment can cause neointimal proliferation.

Brachytherapy can only be used once in each vessel, and long-term DAT with aspirin and clopidogrel is essential, given the risk of late in-stent thrombosis. Ultimately, long-term data are disappointing with a high failure rate; brachytherapy has therefore fallen largely out of favor.

XIV. PHARMACOLOGIC ADJUNCTIVE THERAPY

A. Antithrombins. Antithrombins prevent the generation of thrombin and/or inhibit the activity of thrombin. An antithrombin such as unfractionated heparin (UFH), bivalirudin (direct thrombin inhibitor, DTI), or enoxaparin (low-molecular-weight heparin, LMWH) should be used during all coronary interventions to prevent thrombus formation on the equipment. This principle applies even to patients with a high international normalized ratio (INR). The following provides a brief overview of the anticoagulant agents used during PCI. For specific data regarding their use during ACS, please refer to **Chapter 2**.

B. Unfractionated heparin

1. UFH binds and induces a conformational change in antithrombin, converting it to a more efficient inhibitor of circulating thrombin (factor IIa), factor Xa, factor IXa, factor XIIa, and kallikrein. The typical dose is 60 to 100 units/kg bolus if no GP IIb/IIIa inhibitor is given. If a GP IIb/IIIa inhibitor is given, then 50 to 70 units/kg of heparin is infused as a bolus. No maintenance infusion is given. UFH boluses are given to maintain an ACT of 250 to 300 seconds without concomitant GP IIb/IIIa inhibitor and closer to 200 seconds with GP IIb/IIIa inhibitors. Maintenance of appropriate levels of anticoagulation is imperative to safely navigate the path between thrombosis and bleeding complications.
2. In uncomplicated PCI cases, prolonged postprocedural heparin infusions increase bleeding complications and do not lower the likelihood of abrupt vessel closure or the rate of restenosis. The sheath should be removed when the ACT is < 180 seconds.

C. Low-molecular-weight heparin

1. LMWH results in more predictable factor Xa inhibition. LMWHs are increasingly being used in the setting of ACS, as a result of data suggesting a possible reduction in the combination of recurrent angina, MI, and death associated with the use of enoxaparin as compared with UFH (ESSENCE and TIMI IIb trials).
2. If a hospitalized patient has been given subcutaneous enoxaparin, a reasonable strategy is as follows. If PCI is performed within 8 hours of subcutaneous enoxaparin administration, then no additional heparin is required. If PCI is performed within 8 to 12 hours, an additional IV dose of 0.3 mg/kg of enoxaparin should be administered. If PCI is performed > 12 hours after enoxaparin injection, standard doses of UFH can be used.
3. When using LMWH, ACT measurement does not reflect the degree of anticoagulation and there is no rapid method for determining factor Xa activity. This inability to confirm adequate antithrombin activity and assess the level of anticoagulation with a bedside test makes some interventional cardiologists uncomfortable. Significant anti-factor Xa activity persists for about 12 hours. LMWH is only partially reversed with protamine.
4. Dosing LMWH in obese patients provides a much less reliable level of anticoagulation. Extreme caution should be exercised in patients with moderate-to-severe renal insufficiency (i.e., creatinine clearance < 30 mL/min), as the renal elimination of LMWH may result in unexpectedly high degrees of anticoagulation for a prolonged period. In these cases, most interventionalists will use an alternative antithrombotic agent.
5. Fondaparinux is a synthetic pentasaccharide that binds to antithrombin and induces a conformational change that increases its affinity for factor Xa. Fondaparinux has compared favorably with LMWH in both the NSTEMI and

STEMI settings, in large part due to a significant decrease in bleeding complications. However, there is an increased risk of guide-catheter thrombosis, which requires concomitant administration of UFH (OASIS-8).

D. Direct thrombin inhibitors (bivalirudin)

1. The initial DTI was isolated from leech saliva, although now these materials are synthesized using recombinant technology. These agents directly inhibit clot-bound thrombin without requiring an antithrombin cofactor. DTIs are better able to block both fluid-phase and clot-bound thrombin, which may be particularly important in a thrombus' platelet-rich environment.
 2. A hirudin analog, bivalirudin, is becoming increasingly more common in catheterization laboratories and is an important anticoagulant for patients undergoing PCI. The REPLACE-2 trial compared bivalirudin with the combination of abciximab/UFH in a prospective, randomized, double-blind fashion and found it to be associated with fewer bleeding-associated complications and a statistically noninferior rate of MACEs. Bivalirudin has also shown similar salutary effects in patients with STEMI (HORIZONS-AMI) and NSTEMI (ACUITY). Please refer to **Chapter 2** for details of bivalirudin use in ACS.
 3. Bivalirudin is given as a 1 mg/kg bolus followed by a 4-hour maintenance infusion of 2.5 mg/kg/h and by 0.2 mg/kg/h. A given bivalirudin dose provides a more predictable ACT than does UFH. The half-life is 25 minutes in patients with normal renal function, although in dialysis-dependent patients, the half-life may be as long as 3.5 hours. The maintenance infusion can be discontinued after completion of the coronary intervention. If a vascular closure device is not used, the sheath can typically be removed in 1 to 2 hours, given the drug's short half-life. Unfortunately, the effects of bivalirudin cannot be reversed.
- E. **Warfarin.** Routine warfarin is no longer recommended unless a patient has a mechanical prosthetic valve, atrial fibrillation, or intracardiac thrombus. DAT has proven superior. An INR > 1.6 is a strong relative contraindication to elective cardiac catheterization. If emergent cardiac catheterization is required due to ACS or MI, consider accessing the radial artery because hemostasis is rarely an issue with this approach.

F. Antiplatelet therapy

1. Platelets are essential in thrombus formation, and some form of antiplatelet therapy is typically given at the time of PCI.
2. **Thromboxane A₂ inhibitor (aspirin).** Aspirin impairs platelet aggregation by irreversibly inhibiting platelet cyclooxygenase, thereby limiting thromboxane A₂ production. A loading dose of 325 mg of aspirin should ideally be given at least 2 hours before PCI and be continued at 325 mg daily for at least 1 month following the procedure. In the case of DES, higher-dose aspirin may be continued for longer periods. Secondary prevention trials have shown aspirin to reduce death, MI, and stroke by 27%. In PCI patients, aspirin reduces abrupt vessel closure.
3. **Adenosine diphosphate receptor antagonists (clopidogrel, ticlopidine, and prasugrel)**
 - a. Thienopyridines such as clopidogrel and ticlopidine inhibit adenosine diphosphate–induced platelet aggregation by the P2Y₁₂ receptor. Clopidogrel is preferred to ticlopidine because of its better safety profile, although both require hepatic metabolism for activation.
 - b. Ticlopidine is poorly tolerated with prolonged use, resulting in 20% of patients discontinuing the drug due to nausea, diarrhea, and rash. Neutropenia and thrombotic thrombocytopenic purpura (TTP) occur in 1% to 3% and 0.03% of patients, respectively. The complete blood count should be serially examined in the first several months of use (q2wk × 3 months).
 - c. Clopidogrel is better tolerated than ticlopidine and has largely replaced it in clinical practice in the United States. The risk of TTP with clopidogrel is the

same as in the general population (11 in 3 million), and neutropenia is not an issue, making blood count monitoring unnecessary.

- d. The ACC/AHA guidelines recommend routine clopidogrel pretreatment with a dose of 600 mg, although this recommendation is made on the basis of studies that included patients with ACS. In patients undergoing elective PCI, a recent study revealed no difference in ischemic or bleeding complications between 300 and 600 mg loading doses. Similarly, in patients on chronic clopidogrel therapy undergoing elective PCI, the ARMYDA-4 RELOAD investigators found no benefit to an additional 600 mg “reloading” dose of clopidogrel; the group of patients with NSTEMI did have a reduction in MACE at 30 days, however.
 - e. For a discussion of clopidogrel duration after PCI, please refer to Section **XI.D**. For details of clopidogrel use after ACS, please refer to **Chapter 2**.
 - f. The issue of clopidogrel nonresponsiveness, defined as platelet inhibition < 20%, is reported to be as high as 40% and is associated with worse clinical outcomes including ST, MI, and death. Mechanisms include genetic predisposition (i.e., CYP2C19 polymorphism that affects clopidogrel metabolism and thus activation) and drug–drug interactions (i.e., concomitant proton pump inhibitor use). Unfortunately, recent studies (including OASIS-7 and GRAVITAS) have not shown a benefit to higher maintenance dose clopidogrel (150 vs. 75 mg daily), even in patients with established high platelet reactivity while on clopidogrel. Management of these patients is therefore difficult, but we currently either use double-dose clopidogrel or change to prasugrel in cases of clopidogrel nonresponse.
 - g. Prasugrel is a novel thienopyridine prodrug that requires conversion to an active metabolite with high affinity for the platelet P2Y₁₂ receptor site, resulting in a potent antiplatelet effect. The TRITON-TIMI 38 trial randomized 13,608 patients with moderate-to-high risk ACS with scheduled PCI to either prasugrel or clopidogrel therapy and found a significant reduction in the primary efficacy end point of death from cardiovascular causes, nonfatal MI, or nonfatal stroke associated with prasugrel therapy. Prasugrel was also associated with a reduction in rates of MI, TVR, and ST. However, of some concern was a significant increase in major (HR 1.32, 95% CI 1.03 to 1.68, $p = 0.03$) and life-threatening (1.4% vs. 0.9%, $p = 0.01$) bleeding observed in the prasugrel group.
- G. GP IIb/IIIa inhibitors (abciximab, eptifibatide, and tirofiban)**
1. GP IIb/IIIa receptor inhibition prevents these receptors from binding to fibrin and forming the platelet–fibrin cross-linking that is required for thrombus formation. GP IIb/IIIa receptor occupancy > 80% prevents the development of thrombus.
 2. **Abciximab** is a human–murine chimeric antibody fragment that binds the GP IIb/IIIa receptor with high affinity, resulting in a slow dissociation rate (i.e., noncompetitive inhibition). Although abciximab remains detectable on platelets for the lifetime of the platelet, it is rapidly cleared from plasma, allowing platelet aggregation to return to normal in 12 to 36 hours. Rapid reversal of platelet inhibition in the event of bleeding requires discontinuation of the abciximab infusion, waiting 30 minutes for plasma clearance, and platelet infusion (12 units) so as to provide functional platelets. Profound thrombocytopenia occurs in 0.4% to 1.1% of patients. Platelet counts should be measured within the first 2 to 4 hours and the following day. Abciximab readministration has not been associated with hypersensitivity or anaphylaxis, although the risk of profound thrombocytopenia is somewhat higher (2.2%).
 3. **Eptifibatide** is a cyclic heptapeptide and **tirofiban** is a tyrosine derivative nonpeptide mimetic. Both act as competitive inhibitors requiring high levels for adequate inhibition. Both have a short plasma half-life (2.0 to 2.5 hours), with platelet aggregation normalizing in 30 minutes to 4 hours. In the event of bleeding, the infusion should be stopped. Unlike abciximab, the effect cannot

be reversed and platelets remain inhibited until plasma drug levels fall. Profound thrombocytopenia is rare (0.0% to 0.3%).

4. The use of GP IIb/IIIa inhibitors versus heparin alone during PCI prevents 65 adverse events per 1,000 treated patients and is arguably beneficial for all types of interventions. These benefits are particularly enhanced for unstable angina, diabetes mellitus, and bail-out stenting. Even in the contemporary era of stents and thienopyridines, a recent meta-analysis has demonstrated the reduction in nonfatal MI compared with heparin alone, although there was an increase in minor bleeding.
5. For specific recommendations regarding the use of GP IIb/IIIa inhibitors during ACS, please refer to **Chapter 2**.

H. Intracoronary vasodilators. PCI can result in no-reflow, which is defined as a reduction in coronary flow without an obstructive lesion. The most probable causes of no-reflow are microvascular spasm and distal embolization. Potent microvascular vasodilators, such as adenosine (36 to 72 μ g), nicardipine (100 to 200 μ g), nitroprusside (50 to 200 μ g), or verapamil (200 μ g), often restore normal flow. Nitroglycerin is a logical choice for relieving epicardial spasm but has no effect on the microvasculature. Immediately before SVG intervention, verapamil pretreatment has been shown to prevent no-reflow but has never been shown to reduce the risk of CK-MB elevation.

XV. SUPPORTIVE ADJUNCTIVE THERAPY

- A. The use of percutaneous circulatory support during PCI may be necessary during high-risk intervention or in cases of acute MI presenting with cardiogenic shock. A number of devices exist for this application, although the data supporting their use are scant. Nevertheless, each of these may be appropriate on a case-by-case basis based on the physician judgment. This brief overview will address the use of percutaneous support for elective PCI.
- B. **Intraaortic balloon pump.** There is usually a low threshold for prophylactic IABP insertion in high-risk PCI patients (e.g., poor ventricular function, large area of myocardial ischemia, critical left main trunk disease, and cardiogenic shock). While observational studies have suggested a benefit to this strategy, the only randomized trial comparing prophylactic IABP with bail-out IABP for high-risk PCI found no difference in MACE, MI, death, or hospital discharge. The bail-out group did have a higher rate of hypotension and 12% of patients required “rescue” IABP. Because of the inherent risk of complications, such as atheroembolism, distal limb ischemia, infection, and thrombocytopenia, IABP should be reserved for selected patients in whom there is an appropriate risk/benefit ratio.
- C. **TandemHeart (TH).** The TH system is used for percutaneous LV support and consists of an inflow cannula placed from the femoral vein to the left atrium via trans-septal puncture (21F) and an arterial outflow cannula placed in the femoral artery and parked in the descending aorta (15 to 17F). The device provides up to 5.0 L/min of cardiac output. Among 33 patients with cardiogenic shock, the majority of whom had undergone PCI for acute MI, randomized to IABP ($n = 14$) versus TH ($n = 19$), there was an improvement with TH with respect to cardiac output, pulmonary capillary wedge pressure, and mean arterial pressure. There was no difference in survival, but the number of patients was relatively small. These findings were subsequently corroborated by the ISAR SHOCK trial of TH versus IABP (increase in cardiac index 0.49 vs. 0.11 L/min/m² at 30 min, $p = 0.02$; 30-day mortality in both groups: 46%).
- D. **Impella 2.5 and 5.0.** The Impella device is essentially a pigtail catheter that sits across the aortic valve and draws blood out of the left ventricle and ejects blood into the ascending aorta. The catheter comes in two forms: a 9F device (inserted via a 13F sheath) that supports an output of 2.5 L/min and a 9F system that supports an output of 5.0 L/min. The larger device requires a cut down at the femoral site for placement of the catheter because while the LV portion of the device has a 21F caliber, the shaft is only 9F (so the purse-string suture at the femoral site is cinched around the shaft once the device enters the artery). Registry studies have demonstrated the feasibility

of use of both devices. The PROTECT II randomized trial comparing high-risk PCI (defined as unprotected left main coronary or the last patent conduit and a left ventricular ejection fraction [LVEF] under 35% or three-vessel disease and an LVEF over 30%) supported by prophylactic placement of an Impella 2.5 versus IABP, however, was stopped early due to difficulty in enrolling patients. Of the patients enrolled, there were no significant differences in the two arms at 30 days. The investigators are quick to point out, however, that there were significant differences between the two groups of patients, as the Impella group more often underwent rotational atherectomy and were more likely to have a “complete revascularization” performed.

- E. In contrast to the IABP, which requires at least modest LV function, the two percutaneous left ventricular assist devices (pLVAD; TandemHeart and Impella) can provide support to patients with minimal LV function. The pLVAD may thus be well suited to situations where an IABP has been ineffective, or in patients with hemodynamic catastrophe, as opposed to placement as a first-line means of support.

XVI. POST-PCI MANAGEMENT

A. Access site care

1. The groin or arm access site should be examined for hematoma, pseudoaneurysm (systolic bruit), and arteriovenous fistulas (continuous murmur). A pulsatile mass also suggests a pseudoaneurysm. Ultrasound studies can confirm the diagnosis of pseudoaneurysm or arteriovenous fistula. Suprainguinal tenderness, back pain, lower quadrant abdominal pain, or hypotension should make one suspicious for retroperitoneal hemorrhage, which can be confirmed by computed tomography (CT). A hemoglobin level 1 day after PCI should be routine, and a decrease > 2 g/dL is concerning. Distal pulses should be examined as well. Pulselessness, pain, pallor, paresthesias, and a cool extremity suggest an acute arterial occlusion.
2. **Pseudoaneurysms** < 2 cm often close spontaneously; those 2 to 3 cm can often be closed by external, ultrasound-guided compression (90% success rate); and those > 3 cm generally require surgical correction. Another frequently successful option is thrombin injection if the pseudoaneurysm has a thin neck.
3. **Arteriovenous fistulas** are typically small and inconsequential, rarely causing high-output failure. Indications for ultrasound-guided compression (success rate $> 80\%$) or surgical closure include significant shunting, extremity swelling/tenderness, CHF, and deep venous thrombosis.
4. A **retroperitoneal hemorrhage** can be treated by supportive care (i.e., transfusions, close observation, and bed rest) in $> 80\%$ of cases. Anticoagulation must be reversed, and frequent hemodynamic monitoring in an experienced intensive care unit is required. If required, transportation to CT scan should be deferred until the patient is hemodynamically stable. If the bleeding does not spontaneously stop, the patient may require vascular surgery consultation. Other options include balloon tamponade or coil embolization if a small side branch is the culprit.
5. **Acute arterial occlusion** may be due to dissection or thromboembolism. Both typically require angiography of the affected extremity with access from another extremity (e.g., with a cold right leg after right femoral artery access, left femoral access should be obtained and an angiogram of the right lower extremity can be performed by crossing over to the right common iliac artery). Dissection typically requires prolonged balloon inflation and possible stenting or surgery. Stenting at the common femoral artery is discouraged, because it is a flexion point and a frequent site of attaching bypass grafts. Thromboembolism can be treated with surgical (Fogarty catheter) or percutaneous mechanical thrombectomy (Possis AngioJet).

- B. **Monitoring for myocardial ischemia.** A 12-lead ECG should be obtained before and after PCI in order to have a baseline. The patient should be monitored on a cardiac ward that has continuous electrocardiographic monitoring and nurses familiar with routine post-PCI care. The creatine kinase (CK) and CK-MB levels should be measured 12 hours after the intervention. A procedural MI is presently

defined as a CK-MB more than three times the normal (assuming a normal baseline CK-MB). Elevated CK, CK-MB, or electrocardiographic abnormalities occur in 5% to 30% of patients. Mechanisms include distal embolization, side branch occlusion, dissection, and spasm. Troponin levels are not routinely measured after PCI.

- C. Monitoring for contrast-induced nephropathy.** Nonsteroidal anti-inflammatory drugs, cyclosporine, and metformin should be withheld for 24 to 48 hours beforehand and for 48 hours afterward. Postprocedure saline hydration is continued at 75 to 150 mL/h for a total infusion of 1 to 2 L. Renal function (serum creatinine) should be monitored in patients with diabetes and renal dysfunction.

ACKNOWLEDGMENTS: *The authors thank Dr. Matthew Casey Becker and Dr. Kent Dauterman for contributions to earlier editions of this chapter.*

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Percutaneous Structural Heart Disease Procedures

The last decade witnessed a remarkable rise in the number of novel percutaneous, catheter-based procedures using new concepts and technologies for the treatment of structural heart disease. Most percutaneous therapies have largely evolved from concepts developed by surgeons and often incorporate the lessons learned from established surgical procedures. Currently, percutaneous catheter-based therapy is available for a number of valvular disorders, including aortic stenosis (AS), mitral stenosis (MS), mitral regurgitation (MR), and prosthetic paravalvular leaks (PVLs), as well as other structural cardiac disorders such as hypertrophic obstructive cardiomyopathy (HOCM), patent foramen ovale (PFO), and atrial septal defects (ASDs). While a comprehensive review of structural cardiac interventions is beyond the scope of this chapter, we provide an overview of the major devices and clinical studies that have been performed.

I. PERCUTANEOUS TRANSCATHETER MITRAL VALVE REPAIR (MVRE)

A. Background. MR is one of the most common valvular disorders, encountered in about 7% of the population aged > 75 years. MVRe, when feasible, produces superior outcomes, including lower operative mortality, improved long-term survival, and reduced incidence of endocarditis and thromboembolic complications, compared with mitral valve replacement (MVR). A number of percutaneous MVRe techniques have been developed that are analogous to surgical procedures. Percutaneous mitral annuloplasty leverages the close relationship of the coronary sinus (CS) to the posterior mitral annulus. The **Carillon** (Cardiac Dimensions, Kirkland, WA) device, which has been granted Conformité Européenne (CE Mark) approval, is deployed in the CS and serves to “cinch” the annulus, resulting in improved mitral valve (MV) leaflet coaptation. There are also numerous other devices in various stages of preclinical and clinical development.

The **MitraClip** (Abbott Vascular, Santa Clara, CA) remains the most widely tested system in humans and is currently the only device available (under trial basis) in the United States. A total of more than 4,000 procedures have been performed in the United States (under trial) and Europe (where the device has CE Mark approval). The technique is based loosely on the surgical Alfieri stitch, which brings the anterior and posterior leaflets in close apposition using a suture and creates an anatomic “double-orifice” MV.

B. Procedure. The MitraClip system uses a steerable 22F guide catheter that is introduced through the femoral vein and subsequently advanced to the left atrium via transseptal puncture (Fig. 66.1). Through this guiding catheter, a delivery system containing the V-shaped clip is introduced in the left atrium and positioned with the arms of the clip perpendicular to the MV line of coaptation using transesophageal echocardiography (TEE) guidance. The clip is advanced to the left ventricle in an open position and retracted to grasp the anterior and posterior MV leaflets at the desired location. After confirmation by TEE of clip position, the clip can be locked.

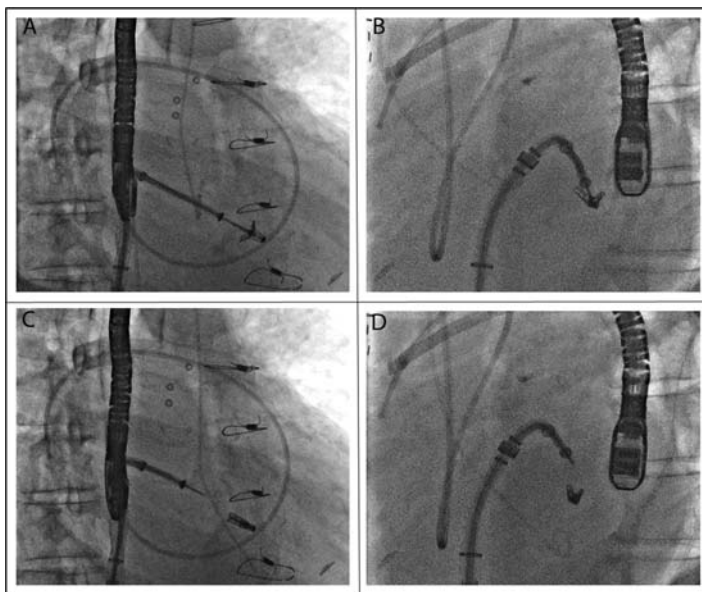


FIGURE 66.1 Percutaneous transcatheter mitral valve repair. Panel A demonstrates the right anterior oblique projection of the optimal positioning of the MitraClip device. Panel B demonstrates the left anterior oblique projection of the optimal positioning of the MitraClip device. Panel C demonstrates the right anterior oblique projection of MitraClip after its release from the delivery catheter. Panel D demonstrates the left anterior oblique projection of MitraClip after its release from the delivery catheter.

If satisfactory (by TEE), the clip can be released; otherwise, it can be reopened and the process repeated. If necessary, multiple clips can be deployed to achieve a satisfactory result. Care must be taken in this situation to not impede forward flow across the valve and trade MR for MS.

- C. Complications.** Routine complications associated with vascular access like major or minor bleeding are the most commonly encountered complications. Recurrent MR and the requirement for MV surgery are the prime limitations of the current technique, especially in ischemic MR or in the presence of a significant annular calcification. Partial clip detachment is the most important mechanical problem encountered with the procedure. These are generally not symptomatic and are treatable with MV surgery or placement of an additional clip. Iatrogenic MS is a significant complication that may arise as a result of this procedure. Careful echocardiographic evaluation of the MV apparatus is important prior to leaflet plication. A coaptation length of at least 2 mm, a baseline MV area of at least 4 cm², and central origin of the regurgitant jet should be ensured prior to the percutaneous repair, to maximize success and avoid complications.
- D. Outcomes.** The edge-to-edge repair technique was tested in the EVEREST I (Endovascular Valve Edge-to-Edge REpair Study) safety and feasibility trial, which demonstrated a 74% procedural success rate (reduction in MR to $\leq 2+$) with a $< 1\%$ inpatient mortality rate. Freedom from death, MV surgery, or MR $> 2+$ was 66% at the end of 1 year. Data from the pivotal EVEREST II trial, which randomized 279 patients to MitraClip versus surgical repair in a 2:1 fashion, demonstrated freedom from the combined end point (death, MV surgery within 90 days, or MR $> 2+$ at

1 year) of 72.4% and 87.8% in the two groups, respectively, confirming noninferiority of the MitraClip to conventional surgical treatment.

The initial studies of the MitraClip concentrated on patients with degenerative disease. However, the EVEREST II trial and the clinical experience in Europe (where the device enjoys the CE Mark) have shown efficacy in a large number of patients with functional MR as well. Freedom from significant MR was enjoyed by more than 80% of high surgical risk patients, with resultant decreases in left ventricular (LV) volume, NYHA class, congestive heart failure (CHF) hospitalizations, and improved quality of life. Percutaneous MVRe procedures still remain investigational in the United States and in the current iterations available are applicable to patients in whom surgery is of relatively high risk, given the excellent outcomes with surgical MVRe in terms of both freedom from reoperation and significant MR and operative morbidity and mortality.

II. PERCUTANEOUS MITRAL BALLOON VALVULOPLASTY (PMBV)

A. Background. Although there has been a significant reduction in the prevalence of rheumatic heart disease in western countries, it still represents a major public health concern in the developing world. MS is one of the most common presentations of rheumatic heart disease. It continues to represent a major clinical problem in the United States primarily due to outmigration from developing countries or the occurrence of restenosis after previous surgical commissurotomy. Stenosis of the valve may occur due to commissural fusion, leaflet thickening, and/or chordal shortening and fusion.

Before the advent of PMBV, symptomatic MS was treated using surgical commissurotomy. Since the introduction of the percutaneous procedure in the early 1980s by Inoue and colleagues, PMBV has evolved to become the first line of therapy for appropriately selected patients with MS. The technique works similarly to commissurotomy, resulting in opening of the fused commissures.

B. Procedure. The Wilkins splitability score is the most widely used echocardiographic parameter to determine the safety and feasibility of PMBV, and this takes into consideration leaflet mobility, leaflet thickening, subvalvular thickening, and valve calcification (each scored 1 to 4 points). Multiple investigators have shown that patients with a score of 8 or less have the greatest freedom from death and valve surgery and the largest improvement in mitral valve area with PMBV.

Selection of the appropriate balloon size is one of the most important steps for accomplishment of a successful PMBV. A good rule of thumb is to use the following formula to determine the maximum balloon dilation size: Balloon size (mm) = patient height (cm)/10 + 10 mm. Sizing of the balloon with contrast inflation is confirmed *ex vivo* using a measurement device (provided). We routinely perform the procedure as follows: a 5F arterial access is obtained in order to obtain left ventriculography to understand the position of the MV and commissural anatomy in the fluoroscopic projection. Transseptal puncture is performed (most commonly with TEE guidance) using the standard Brockenbrough needle via a 9F Mullins sheath placed in the femoral vein. Once the sheath has entered the left atrium, it is exchanged for the Inoue balloon catheter.

The balloon catheter is slowly advanced into position in the left ventricle. The Inoue balloon consists of three portions with slightly different compliances. As pressure is added to the balloon, the distal portion inflates first followed by the proximal portion. As soon as the distal portion is inflated, the balloon is pulled until resistance is felt. On addition of more pressure, the proximal portion is inflated, which fixes the valve in the middle waist portion of the valve. The middle waist has the least compliance and dilates only when substantial pressure is added to the balloon, thereby securing the balloon across the valve prior to the dilation of the annulus.

In our institution, we routinely use TEE to guide the valvuloplasty in order to assess the result of balloon inflation (in addition to simultaneous left atrial [LA]–LV

gradient measurement) and, more importantly, to evaluate the degree of MR. Substantial increases in MR should preclude further inflation. In addition, the procedure should be aborted in the presence of left atrial appendage (LAA) clot. Some institutions have gained facility in using intracardiac echocardiography (ICE) in this application.

- C. **Complications.** The most common serious complications include hemopericardium or severe MR. Perforation of cardiac chambers, which occurs with a rate of 0% to 2%, may happen while manipulating the catheters in the heart. While an increase in MR may routinely be noted after the PMBV, it rarely requires a surgical intervention.
- D. **Outcomes.** Immediate postprocedural success with a final valve area $> 1.5 \text{ cm}^2$ without moderate or severe MR is the best predictor of long-term outcome. The best results are obtained in young people with favorable anatomic characteristics. Randomized clinical trials have demonstrated that long-term results of PMBV in young patients are as good as open commissurotomy and are better than closed commissurotomy. In patients with optimal morphology, freedom from restenosis has been reported as 92% at 5 years, 85% at 10 years, and 65% at 15 years. Repeat PMBV has been recommended as first-line therapy in patients with symptomatic mitral restenosis after PMBV or commissurotomy in whom the mechanism of restenosis is commissural fusion.

III. BALLOON AORTIC VALVULOPLASTY (BAV)

- A. **Background.** Degenerative or calcific AS is one of the most common valvular disorders encountered in western countries. Surgical aortic valve replacement (SAVR) is the treatment of choice for patients who are safely able to undergo cardiac surgery, and transcatheter aortic valve replacement (TAVR) is emerging as a favorable option in patients at high risk for surgical complications. Balloon dilation of the calcified aortic valve results in stretching of the fused commissures. Due to rapid reversibility of these effects, there is an early loss of effectiveness in severe degenerative AS, and the valve returns to pre-BAV size in 3 to 6 months.

In patients with severe AS who are hemodynamically unstable and for whom urgent aortic valve replacement (AVR) is not feasible, BAV may serve as a “bridge” to valve replacement. Similarly, we have also seen significant functional improvement in patients after BAV so that patients unable to undergo AVR initially have improved to a point that TAVR or SAVR could be performed safely. In patients who require urgent noncardiac surgery, BAV may be considered as a temporizing measure in the hope of reducing the risks of perioperative hemodynamic changes associated with anesthesia.

A number of patients with severe AS have other comorbidities, such as chronic obstructive pulmonary disease or liver or kidney disease, that make it difficult to discern the degree to which AS contributes to their symptoms. In such cases, BAV may provide a therapeutic answer; improvement of symptoms points to AS as the driver of symptoms and may push for a more definitive valve replacement option. Finally, in patients without any option for either TAVR or SAVR, BAV may be considered as a palliative measure.

- B. **Procedure.** The femoral retrograde approach is the most commonly utilized method for BAV, although in patients with severe iliofemoral disease the procedure can be performed in an antegrade fashion via venous access and transseptal puncture. A Swan-Ganz catheter is placed in the pulmonary artery for continuous hemodynamic monitoring and assessment of cardiac output. A temporary pacemaker is placed in the right ventricle to perform rapid pacing (180 beats per minute) during balloon inflation to reduce cardiac output and minimize balloon movement in the annulus. After crossing the aortic valve using a 5F AL-1 diagnostic catheter and a straight wire, a stiffer wire is inserted and positioned in the left ventricle. BAV is typically performed using balloons ranging from 15 to 25 mm in diameter. The balloon is sized based on the annulus diameter on transthoracic echocardiography

(TTE); the maximum balloon size is 10% larger than the annulus, and we routinely begin dilation at smaller sizes and assess the hemodynamic result prior to increasing the balloon size. Procedural success with BAV is typically defined as a 50% reduction in mean aortic valve gradient and a 25% increase in aortic valve area (AVA); most patients usually experience almost a 50% increase in AVA.

- C. Complications.** It should be noted that BAV carries considerable risk. The 30-day mortality associated with the procedure may be up to 10%, usually due to either aortic regurgitation (as a complication of the balloon procedure) or persistent heart failure. Other complications (occurring in up to 15%) include stroke, peripheral vascular complications (due to the size of the devices used and concomitant incidence of peripheral arterial disease), coronary occlusion, need for permanent pacemaker implantation, cardiac tamponade, and cardiac arrest.
- D. Outcomes.** Despite a modest improvement in valve area, a significant improvement in the functional status is noted after BAV. However, the benefit of BAV gradually disappears over the course of the next few months. The poor functional status of the patients, as well as only moderate, transient effects of the technique, is primarily responsible for the overall grim long-term results of stand-alone BAV. Although there are no contemporary studies comparing SAVR with BAV, extensive data indicate that stand-alone BAV does not change the natural course of AS, even after repeated procedures. Despite this, BAV holds an important place in the treatment of patients with severe AS. In our current experience, BAV is most often performed to bridge severely symptomatic patients to TAVR or SAVR or to better understand the contribution of AS to functional limitation in patients with multiple comorbidities. BAV has tremendous potential to alleviate symptoms and provide an opportunity for functional improvement that allows definitive treatment with AVR and improved quality and quantity of life in patients with severe AS.

IV. TRANSCATHETER AORTIC VALVE REPLACEMENT

- A. Background.** Up to a third of patients with severe symptomatic AS do not undergo surgical AVR, as they are deemed to have a high surgical risk due to age or multiple comorbidities. The interest in percutaneous aortic valve implantation began in the early 1990s. The first human experience was reported by Cribier et al. in 2002. Since then, rapid advancements in the design of the stented valve and delivery catheters and improved facility in implantation techniques have led to a consistent improvement in the postprocedural outcomes and have heralded a new era in the treatment of valvular AS.

The procedure involves implantation of a tissue pericardial valve that is mounted within a stent. The key to TAVR success is a careful selection of patient population for the procedure and a judicious use of preprocedural and intraprocedural imaging modalities, including fluoroscopy and aortic angiography.

Currently, the indications for TAVR include severe symptomatic AS with a valve area of $\leq 0.8 \text{ cm}^2$, mean aortic valve gradient of $\geq 40 \text{ mm Hg}$, or a peak aortic jet velocity of $\geq 4.0 \text{ m/s}$ with one or more of the following:

- (1) High risk for conventional AVR (Society of Thoracic Surgeons score > 10 or logistic EuroSCORE $> 20\%$) (web site 209.220.160.181/STSWebRiskCalc/).
 - (2) Contraindication to standard thoracotomy including prior multiple thoracotomies or radiation to the chest wall.
 - (3) Porcelain aorta.
- B. Procedure.** Two types of stented valves have been tested in humans: the balloon-expandable Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and the self-expanding CoreValve ReValving system (Medtronic Inc., Minneapolis, MN) (Fig. 66.2).
- 1. Edwards SAPIEN.** The largest human experience is with the Edwards Lifesciences series of balloon-expandable aortic valves. The valve consists of a tubular

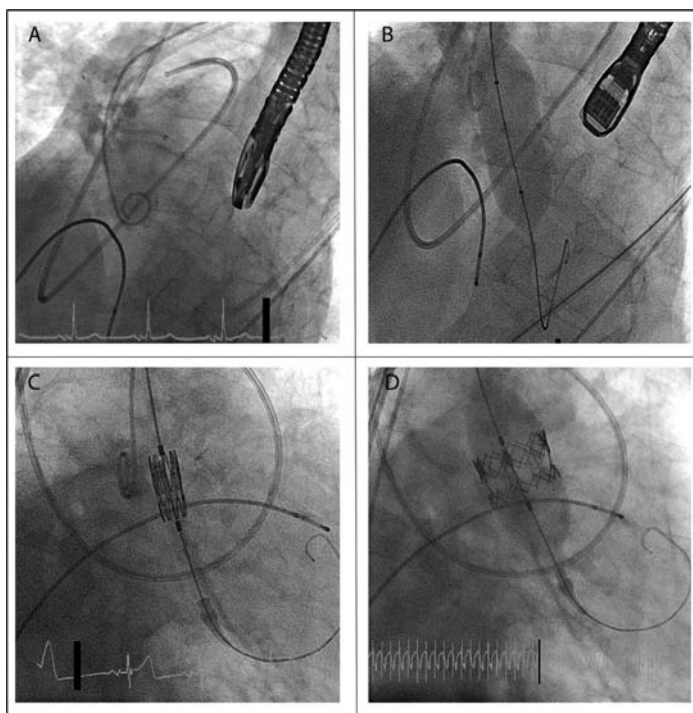


FIGURE 66.2 Transcatheter aortic valve replacement. Panel A demonstrates proper positioning of various catheters and devices for valve replacement: a transesophageal echocardiography probe in the esophagus, a Swan-Ganz catheter in the pulmonary artery, a pigtail catheter in the aortic root, AL-1 diagnostic catheter in the ascending aorta (prior to valve crossing), and a temporary pacemaker wire in the right ventricle. Panel B demonstrates aortic valvuloplasty being performed using a standard balloon. Panel C demonstrates proper positioning of the crimped Edwards SAPIEN prosthesis across the aortic valve. Panel D demonstrates the deployment of the valve using balloon inflation after initiation of rapid pacing.

stainless steel stent with a fabric valve cuff and contains valve leaflets derived from bovine pericardial tissue. This valve is available in two sizes, 23 mm (via 22F sheath access) and 26 mm (via 24F sheath access), and refers to the fully expanded internal stent diameter. Generally, a 23 mm valve is implanted in annuli that measure 18 to 22 mm, and a 26 mm valve is implanted in annuli that measure 23 to 26 mm. Although the valve was implanted initially using the transvenous access and subsequent transseptal puncture, it is now routinely implanted using either a retrograde transfemoral approach or an antegrade transapical approach. Furthermore, the newest iteration of the valve, the SAPIEN XT, which consists of a cobalt chromium stent and allows a smaller sheath size for insertion (18F for 23 mm valve and 19F for 26 mm valve), is currently in use in the Placement of Aortic Transcatheter Valves (PARTNER) II study.

The preprocedural assessment consists of TTE, iliofemoral contrast angiography or iliofemoral computed tomography, and coronary angiography. An iliofemoral diameter of at least 8 mm is required for implantation of the larger Sapien valve,

7 mm for the smaller Sapien valve, and 6 mm for the Sapien XT or CoreValve devices. Appropriate patient selection, which includes the anatomic characteristics of the aortic annulus and iliofemoral system, is imperative to procedural success.

- a. **Transfemoral TAVR.** Transfemoral TAVR is usually performed under general anesthesia in a catheterization laboratory or hybrid operating room equipped with multimodality imaging equipment. Vascular sheaths are placed in a standard fashion in both femoral arteries and veins. Establishing early contralateral arterial and venous access is useful in case of iliofemoral trauma requiring emergency crossover endovascular repair or in case of the need to emergently establish a cardiopulmonary bypass circuit. A transvenous pacing wire is introduced into the right ventricle through the venous access port to enable rapid pacing (180 beats per minute) in order to minimize cardiac output and valve movement during valve deployment. An aortic angiogram is performed to delineate the aortic root anatomy and to facilitate optimal valve positioning. A BAV is then performed using standard technique, with a balloon that is slightly smaller than the size of the planned valve prosthesis.

After routine sheath placement, the femoral access site is “preclosed” using either a Prostar device or two perpendicularly placed Perclose ProGlide devices (Abbott Vascular, Santa Clara, CA). The site is then sequentially dilated to allow placement of either a 22F (for 23 mm valve) or a 24F (for 26 mm valve) arterial sheath. The valve is crimped onto a balloon affixed to a steerable guiding catheter and advanced to the aortic root under fluoroscopic guidance. Once a suitable position is confirmed using fluoroscopy, aortic angiography, and TEE, rapid pacing is initiated and the valve is deployed by inflating the balloon. The final positions of deployment as well as degree of paravalvular aortic regurgitation are assessed using TEE.

Inappropriate positioning may require a second valve deployment. Excessive paravalvular aortic regurgitation may be treated using further balloon dilation or deployment of a second valve. TEE and angiographic assessment for complications (including pericardial effusion, aortic root trauma, and coronary occlusion by the valve) are imperative prior to closure of the femoral access. Similarly, angiography of the iliofemoral system is necessary to evaluate for vascular trauma that might require endovascular or open surgical repair prior to completion of the procedure.

- b. **Transapical TAVR.** Transapical TAVR is indicated in patients with significant narrowing of iliofemoral vessels and who otherwise meet criteria for TAVR. Preprocedural imaging as well as the valve sizing is similar to the transfemoral TAVR described above. After induction of general anesthesia, a 5 to 8 cm anterolateral thoracotomy incision is made to enter the pleural space, directly overlying the apex. The pericardium overlying the apex is opened and a thin portion of the ventricular apex is identified using palpation and TEE. Paired orthogonal U-shaped sutures are placed into the ventricular myocardium and subsequently passed through tensioning tourniquets. Taking due precaution to avoid entry of air into the left ventricle, a 7F sheath is placed into the LV cavity through the apex. A stiff wire is introduced into the sheath, passed across the aortic valve, and positioned into the descending aorta. Femoral access is utilized to place a pigtail catheter into the ascending aorta for aortic root angiography as required. The 7F sheath is upsized to a 14F sheath and aortic valvuloplasty is performed. Subsequently, the 14F sheath is exchanged for a 24F sheath. The mechanically crimped prosthesis is subsequently introduced using a balloon-tipped steerable catheter through this larger sheath and positioned across the aortic valve. After confirmation of optimal positioning using multimodality imaging, rapid pacing is initiated, and the valve is deployed by balloon inflation.

The sheath is then removed and hemostasis is secured with the previously placed sutures. Subsequently, the pericardium is approximated, drainage tubes are placed, and the chest incision is closed.

- 2. CoreValve ReValving system.** The CoreValve system is a self-expanding porcine prosthesis mounted within a nitinol frame and is available in two sizes: 26 mm (intended for annuli 20 to 23 mm) and 29 mm (intended for aortic annuli 24 to 27 mm). The current third-generation device is delivered through an 18F system, commonly via transfemoral and rarely via trans-subclavian or transapical approaches. The general principles involved in the implantation of the valve are similar to balloon-expandable stent implantation. One specific difference in the two devices is that the CoreValve can be repositioned if initial placement is unsatisfactory.
- C. Complications.** Procedural success has ranged from 86% to 100% across the literature. After an initial learning curve, excellent procedural success rates with minimal intraprocedural mortality have been reported at major tertiary care centers performing TAVR. Vascular access complications are encountered more often (16% to 18% patients) than with other interventional procedures due to the large sheath sizes used for TAVR. Complications associated with limited thoracotomy are expected after transapical TAVR. Malposition of the aortic prosthesis may be encountered in about 1% to 3% of cases. Periprocedural strokes have been reported in 4% to 7% of patients undergoing TAVR with an Edwards SAPIEN valve and about 3% with the CoreValve prosthesis. Major complications following CoreValve implantation include the need for permanent pacemaker implantation in up to one-third of patients.
- D. Outcomes.** The PARTNER trial was the first multicenter randomized controlled trial of TAVR and provided two important randomized comparisons. Cohort B compared the outcomes in 358 patients with severe symptomatic AS who were unsuitable for surgery and were randomized to standard therapy including BAV versus TAVR with the Edwards SAPIEN valve. All-cause mortality at the end of 1 year was 30.7% in the TAVR group versus 50.7% with standard therapy ($p < 0.001$). Cohort A compared the outcomes in 699 high-risk AS patients randomized to TAVR versus surgical AVR. There were no significant differences in 30-day or 1-year mortality between the two groups; however, there were important differences in periprocedural complications. The TAVR group encountered a higher rate of stroke and vascular complications, and the surgical AVR group encountered a higher rate of atrial fibrillation (AF) and major bleeding.

Several prospective studies reported similar benefits using the CoreValve prosthesis. A large prospective registry of 663 patients undergoing TAVR with the third-generation CoreValve reported procedural success of 98%, with intraprocedural mortality of 0.9%. The cumulative incidence of mortality was 5.4% at 30 days and 15.0% at 1 year. Major complications after CoreValve implantation included post-procedural PVL (21%) and the need for a permanent pacemaker (10% to 33%).

Based on the encouraging results of PARTNER Cohort B, the Edwards SAPIEN valve was recently granted US FDA approval for use in inoperable patients. The CoreValve is still available for use in the United States only under the auspices of a clinical trial. Both valve systems have been granted CE Mark approval. A number of other valve systems are currently in various phases of preclinical and clinical development.

V. PFO CLOSURE

- A. Background.** PFO is a remnant of fetal cardiac circulation and is found in 27% to 33% of adults. Although generally believed to be an “innocent bystander,” PFO has been associated with stroke, migraines, platypnea-orthodeoxia, and decompression sickness among divers. PFO arises when the septum primum and septum secundum fail to fuse despite some degree of overlap. Atrial septal aneurysms and prominent Chiari networks have been associated with PFO. Percutaneous PFO closure is currently recommended in patients with platypnea-orthodeoxia and in divers with decompression sickness. Although several observational studies have shown the

benefits of PFO closure in the prevention of migraine and cryptogenic strokes, these findings have not been confirmed in major randomized trials. Hence, controversy persists regarding definitive indications and settings for PFO closure for migraine and cryptogenic stroke prevention.

All PFO closure devices have a similar design, usually consisting of two atrial disks connected by a short neck. Under fluoroscopic and ICE guidance, the device is placed such that the two atrial disks lie on either side of the interatrial septum, with the neck positioned in the PFO tunnel. A large part of the atrial shunt is eliminated as a result of physical obstruction to flow. Most of the residual shunt is eliminated over the course of a few months after the procedure, as the device becomes endothelialized. Dual-antiplatelet therapy is generally recommended for the first 6 months after closure to minimize the risk of thromboembolism prior to device endothelialization.

- B. Procedure.** Several devices for transcatheter PFO closure have been tested in humans, including the Helex septal occluder device (WL Gore & Associates, Newark, DE) and the Amplatzer cribriform ASD occluder device (AGA Medical, Golden Valley, MN) (Fig. 66.3). As these devices are FDA approved only for ASD closure, use for PFO closure is “off-label.” Sizing of the devices may vary based on the degree of associated atrial septal aneurysm; significant aneurysm generally requires a larger device.

Briefly, the procedure involves placement of an 8F to 12F vascular sheath (depending on device size) in one femoral vein and a 9F sheath in the contralateral femoral vein

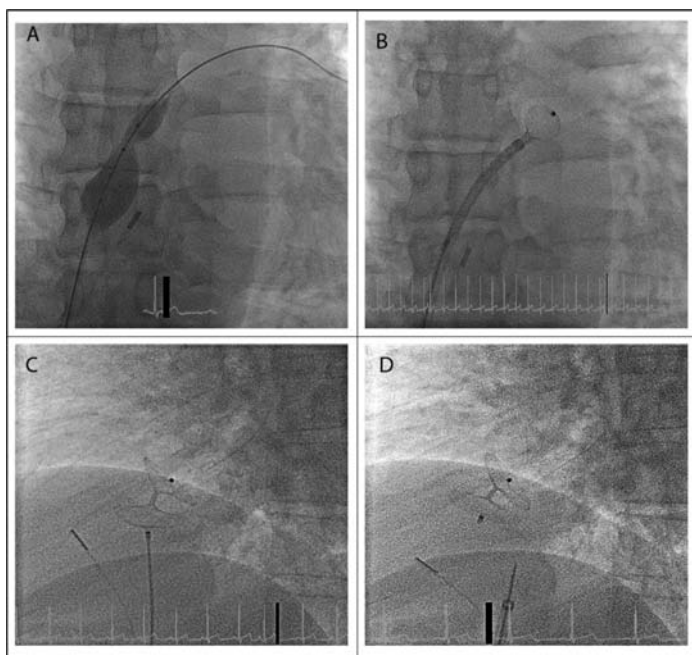


FIGURE 66.3 Patent foramen ovale closure using Amplatzer device. Panel A demonstrates balloon sizing of the PFO tunnel after crossing the PFO using a wire. The intracardiac echocardiography probe is visible next to the balloon. Panel B demonstrates deployment of the left atrial disk of the Amplatzer occluder device. Panel C demonstrates the deployment of the right atrial disk of the Amplatzer occluder device. Panel D demonstrates the device in place after its release from the delivery catheter.

for ICE. The ICE catheter is parked in the right atrium for procedural visualization. The PFO is usually crossed using a wire and a Goodale-Lubin (GL) catheter under ICE and fluoroscopic guidance. Through the GL catheter parked in the left superior pulmonary vein, the wire is exchanged for a stiffer wire over which the closure device delivery system is advanced. The LA disk of the device is deployed and the system slowly retracted. This action facilitates apposition of the septum primum to the septum secundum and effectively closes the PFO. The right atrial disk is then deployed. After confirmation of positioning and stability using ICE and fluoroscopy (and sometimes right atrial angiography), the device is released from the delivery catheter.

- C. Complications.** Transcatheter PFO closure is generally associated with a high procedural success rate and without significant risk of complication. Rare complications including device migration or embolization, symptomatic air embolism, and AF or chamber perforation with cardiac tamponade may occur intraprocedurally. Later complications associated with the procedure include thrombus formation (more common with CardioSEAL than Amplatzer), device erosion, or formation of a new ASD.
- D. Outcomes.** Several large observational studies have demonstrated benefit of PFO closure in secondary prevention of migraine and prevention of recurrent neurological thromboembolism in patients with cryptogenic stroke or transient ischemic attack (TIA). However, these findings have not been ratified in randomized clinical trials. The Migraine Intervention with StarFlex Technology (MIST) study failed to demonstrate any significant difference in migraine cessation between the closure and the “sham” arms. The preliminary results of the randomized controlled trial (CLOSURE I) comparing transcatheter PFO closure with the StarFlex device and optimal medical therapy in patients with cryptogenic thromboembolism failed to demonstrate any significant difference in the rate of recurrent stroke or TIA at the end of 2 years of follow-up in the transcatheter closure group (5.9%) and medical therapy (7.7%) ($p = 0.3$). It has been argued that the inclusion criteria may have been too liberal, however, and therefore could not show a significant difference between the two groups. Furthermore, the procedure was performed using the StarFlex device, which has since been taken off the market due to poor performance and increased risk of adverse events such as thrombus formation. Percutaneous closure of PFO is reasonable in certain clinical scenarios, and a thorough workup is necessary for appropriate patient selection.

VI. ASD CLOSURE

- A. Background.** ASD is one of the most common adult congenital heart diseases encountered in the US population. Although ASDs generally remain asymptomatic till early adulthood, they are associated with several clinical presentations, including right ventricular failure, atrial arrhythmias, pulmonary hypertension, and paradoxical embolism.

Patients with hemodynamically significant ASD should undergo elective closure either surgically or with the transcatheter technique. The hemodynamic significance of an ASD is determined by the presence of right ventricular enlargement in the presence of defect diameter > 1 cm or the presence of significant left-to-right shunting with an elevated shunt ratio ($Q_p:Q_s > 1.5$).

The principle of ASD closure is similar to that of PFO closure, entailing implantation of an occlusion device with atrial disks lying on either side of the interatrial septum and the central waist residing in the ASD. Due to significant variations in size and anatomy of ASD, transcatheter ASD closure is technically more challenging than PFO closure.

- B. Procedure.** Several devices have been used for percutaneous ASD closure. The Amplatzer atrial septal occluder (AGA Medical, Golden Valley, MN) has the largest reported human experience. The other major device available is the Helex (WL Gore & Associates, Newark, DE). The CardioSEAL and StarFlex occlusion devices (NMT Medical, Boston, MA) have been removed from the market due to adverse events.

The procedural approach to percutaneous ASD closure is similar to the percutaneous PFO closure approach as described above. A few important differences exist that are worth considering.

1. Due to a significant variation in the size of ASD and the shape of the defect, proper invasive balloon sizing (by ICE and fluoroscopy) is needed. Both oversizing and undersizing of the device may be hazardous and may lead to complications like device erosion or device embolization.
 2. Device deployment and orientation during transcatheter ASD closure poses greater technical challenges than during PFO closure. The technical complexities are more frequent when ASDs are associated with other structural anomalies like atrial septal aneurysms or in cases of inadequate rim capture. It is imperative to demonstrate an adequate rim surrounding the defect for percutaneous closure.
 3. Multiperforated septa demonstrate a particularly greater challenge to complete closure. In these cases, specific devices like the Amplatzer cribriform occluder or multiple devices may be needed to achieve a good clinical result.
 4. The Amplatzer device is sized based on the defect size (i.e., 16 mm device for a 16 mm ASD) and can be used to close defects 2 to 38 mm in diameter. The Helex device is sized two times the size of the defect (i.e., 30 mm device for a 15 mm ASD) and can be used to close defects 2 to 17 mm in diameter.
- C. Complications.** As in transcatheter PFO closure, procedural success in experienced hands is high and complications are rare. Potential complications include device embolization, tamponade as a result of device erosion into the atrial or aortic wall, residual shunting, or atrial arrhythmias. ASD device mismatch is encountered in 2% to 5% of cases. Other rare complications include vascular access complications, sizing balloon rupture, and entrapment of right atrial structures. Chest discomfort or new onset of arrhythmia may be clues to device erosion or embolization and should prompt urgent echocardiographic evaluation.
- D. Outcomes.** Most patients demonstrate improved functional class and exercise capacity after a successful closure. Several observational studies have demonstrated an improvement in overall long-term survival. Timely ASD closure prevents the development of right heart failure and pulmonary hypertension. There has been evidence of reduction in the size of enlarged cardiac chambers with normalization of intracardiac pressures after successful ASD closure.

VII. VENTRICULAR SEPTAL DEFECT (VSD) CLOSURE

- A. Background.** Although isolated VSDs are a relatively common form of adult congenital heart disease, congenital VSDs of hemodynamic significance are rare, with a prevalence of 0.03% in the adult US population. More commonly, VSDs are acquired as a result of complication of MI, cardiovascular surgery, or chest trauma. Postinfarction ventricular septal rupture (VSR) is associated with > 90% mortality if left untreated. The postinfarction or traumatic VSRs may be located in the posterobasal (inferior infarct) or apical (anterior infarct) portions of the muscular ventricular septum and are typically irregular with multiple ruptures in necrotic myocardium that are prone to rupture or expansion. This presents significant challenges with respect to surgical as well as transcatheter repair.

Percutaneous VSD/VSR closure involves devices that are similar to those described for ASD closure. The device is positioned under fluoroscopy and echocardiographic guidance (TEE and/or ICE as needed) such that the two disks lie on either side of the ventricular septum and the waist lies in the septal defect. The width of the connecting waist determines device sizing.

- B. Procedure.** There are two devices that are approved for closure of congenital muscular VSDs: the CardioSEAL (NMT Medical, Boston, MA) and the Amplatzer muscular VSD occluder device (AGA Medical, Golden Valley, MN). There is a specially designed Amplatzer postinfarction muscular VSR occluder device, which is currently under investigation in the United States. It is similar to its congenital counterpart, except for a longer waist,

large disk diameter, and a larger waist diameter. In patients with postinfarct VSR, it may be necessary to use an atrial septal occluder, as the distance between the disks of the VSD occluder device may be too large. Again, this would be considered an “off-label” usage.

VSD closure can be achieved via the retrograde approach from the left ventricle or via the femoral or jugular vein. The VSD is crossed using a diagnostic catheter and wire, with the wire then externalized to the artery (if approached from the right ventricle) or vein (if approached from the left ventricle) to create a continuous arteriovenous (AV) loop. A delivery catheter containing the device is subsequently delivered over the loop. Under fluoroscopic and echocardiographic guidance, proper alignment and position are confirmed and the device is subsequently deployed.

- C. Complications.** The major complications of transcatheter VSD closure include device embolization, air embolism, residual shunting, defect enlargement, complete heart block requiring pacemaker implantation, arrhythmias, valvular regurgitation due to impingement, and intravascular hemolysis.
- D. Outcomes.** The results of transcatheter closure of congenital VSDs are encouraging; however, the closure of postinfarction VSR has yielded disappointing results in several studies. Although surgery has been recommended as the gold standard for the repair of postinfarction VSD, emergent surgical repair carries an operative mortality of about 50%. This often leads surgeons to recommend delaying the surgery for at least 2 weeks after the initial ischemic event, which may result in a lesser operative mortality and improve the chance of success. Due to this, several centers have attempted transcatheter VSR closure in patients who are either not surgical candidates or too unstable to survive the “waiting period.” Data from observational studies have reported variable success, with mortality rates ranging from 20% to 100%.

VIII. LAA OCCLUSION

- A. Background.** AF is associated with 15% of all ischemic strokes. Autopsy studies have shown that up to 90% of the thrombi in nonvalvular originate in the LAA. Although warfarin has been demonstrated to reduce the rate of stroke in patients with AF, there are several limitations, including risk of bleeding, pharmacologic interactions, and need for prothrombin time (international normalized ratio [INR]) monitoring. In several patients, the use of warfarin may be contraindicated, necessitating another method of stroke prevention.

The LAA orifice is located between the left ventricle and the upper left pulmonary vein, extending over the atrioventricular groove toward the left circumflex coronary artery. Surgical amputation and exclusion of the LAA have been demonstrated to reduce the risk of stroke after MV surgery, without any significant impact on the rate of postoperative AF. In addition, LAA exclusion performed thoracoscopically by stapling the base of the LAA was found to be efficacious in small observational studies. Given the favorable location of the LAA for percutaneous closure, a number of methods have been developed.

- B. Procedure.** There are three devices with significant human experience available for LAA occlusion: the Percutaneous LAA Transcatheter Occlusion (PLAATO) device (ev3, Plymouth, MN), the Amplatzer Cardiac Plug (ACP) (AGA Medical, Golden Valley, MN), and the WATCHMAN device (Altritech Inc., Plymouth, MN). The WATCHMAN and ACP devices have CE Mark approval. The PLAATO device is available in several sizes ranging from 15 to 32 mm, the ACP device ranges from 16 to 20 mm, and the WATCHMAN device is available from 21 to 33 mm. The size and the shape of the LAA should be determined using TEE. Generally, the PLAATO device should be oversized by 20% to 40% and the WATCHMAN device by 10% to 20% for a good result.

The devices are generally implanted using 14F femoral venous access. A trans-septal puncture is performed under fluoroscopic and TEE guidance. The device delivery system allows for collapse, repositioning, or removal of the device in case of unsatisfactory result. Adequacy of the LAA occlusion (defined as mild to absent leak) is confirmed using radiopaque contrast injection into the LA cavity.

- C. Complications.** The complications of the procedure include pericardial effusion, cardiac tamponade, residual leakage, or major vascular complications requiring transfusion.
- D. Outcomes.** In a large series of AF patients undergoing LAA occlusion with PLAATO, the observed annual stroke rate was 2.2%, which represented a 65% relative risk reduction with the PLAATO device. Similarly, the PROTECTion in patients with Atrial Fibrillation (PROTECT-AF) trial has demonstrated the non-inferiority of the WATCHMAN device compared with warfarin therapy for stroke prevention in patients with nonvalvular AF, despite a small increase in periprocedural complications in the device group. The WATCHMAN continued access registry demonstrated a substantial learning curve, with a reduction from 5.0% to 2.2% for pericardial effusion and 0.9% to 0.0% for stroke and increase from 89% to 95% for procedural success. By the same token, medical comparator groups are not ideal, with only half of patients in the PROTECT-AF trial demonstrating therapeutic INR. As with all other procedures, patient selection will be important to maximize benefits until we have a better sense of safety and outcomes.

IX. ALCOHOL SEPTAL ABLATION (ASA). Septal myectomy is considered the gold standard for the treatment of HOCM. ASA has emerged as an attractive, less invasive alternative to myectomy for HOCM that is applicable to those patients who cannot or do not want surgery. Over the last 15 years, the number of ASA procedures done worldwide has surpassed the total number of myectomies performed in the last 50 years. ASA may be considered in patients who have clear evidence of septal hypertrophy (> 18 mm) projecting into the left ventricular outflow tract (LVOT), patients who have dynamic LVOT obstruction (gradient > 50 mm Hg at rest or upon provocation), and patients who have been refractory to medical therapy. Patients with coexistent abnormalities of mitral apparatus are best treated by surgery rather than ASA.

Selective coronary angiographic studies have demonstrated that the septum contributing to the LVOT obstruction is often supplied by the first septal perforator arising from the left anterior descending coronary artery. ASA entails creating a controlled myocardial necrosis by injecting alcohol into the first septal perforator. Postablation, the LVOT gradient demonstrates a triphasic response. There is an immediate reduction in the LVOT gradient after a successful procedure, attributable to the loss of septal contractility and myocardial stunning. Over the next few days, there is an increase in the LVOT gradient due to recovery of the stunned myocardium. The more permanent decrease in LVOT gradient happens over the course of the next few months secondary to myocardial thinning and septal remodeling.

A. Procedure. ASA is performed via femoral arterial access. A guiding catheter is introduced into the left main coronary artery and a guidewire advanced to the septal perforator of interest. Subsequently, a short “over the wire” (OTW) balloon is advanced to the septal perforator and inflated to obstruct backflow of alcohol from the septal to the left anterior descending artery. Angiographic contrast is injected through the balloon to ensure that there is absolutely no backflow into the LAD. Since transient heart block is common during the procedure, a temporary pacemaker is usually inserted.

Echocardiographic contrast is then injected through the OTW balloon in order to map the myocardium that would infarct as a result of ASA. This is an important step, as it helps determine the appropriateness of the procedure and helps in selecting the optimal branch for alcohol injection. Subsequently, 1 to 2 cc of alcohol is injected slowly through the balloon, with the balloon staying inflated for 5 minutes. Intravenous analgesia should be administered, as alcohol injection causes a short-lived but intense discomfort. The balloon is then deflated and removed. A final coronary angiogram is performed to verify lack of septal flow, and echocardiographic gradient is reassessed.

B. Complications. Besides the routine vascular complications that may arise in any interventional procedure, new-onset right bundle branch block is a significant complication of this procedure and is reported in up to 50% of patients in some

series. Complete heart block requiring a need for a permanent pacemaker may occur in about 10% of patients undergoing ASA. The other potential long-term complication includes ventricular arrhythmias, hypothesized to arise as a result of creation of arrhythmogenic myocardial scar. Recent meta-analyses have failed to demonstrate significant differences in ventricular arrhythmias between myectomy and ASA.

- C. Outcome.** Although there are no randomized comparisons between septal myectomy and ASA, large meta-analyses of observational data indicate no significant differences between the two modalities in terms of mortality and improvement in functional status postprocedure. The caveat of ASA is an increased incidence of conduction abnormalities and a small yet significantly higher LVOT gradient postprocedure.

X. PERCUTANEOUS PVL CLOSURE

- A. Background.** PVL is a rare but serious complication that may arise after surgical MVR or more rarely after SAVR. Although most PVLs are small and remain relatively asymptomatic, more than 10% of patients undergoing MVR or SAVR may develop large symptomatic PVLs with serious clinical consequences such as heart failure, endocarditis, or hemolytic anemia. Most PVLs become clinically apparent within 1 year after valve surgery, but a significant proportion may not require any definitive treatment till later. Several risk factors, including extensive annular calcification, evidence of endocarditis, large atria, renal failure, and older age, have been identified that may predispose a valve to develop PVL postsurgery.

Surgical intervention is typically the standard of care in management of patients with symptomatic PVL; however, reoperation is associated with a mortality rate of approximately 16%. Transcatheter closure of symptomatic PVL in a relatively small number of high-risk patients has been attempted in several centers over the last two decades. The devices approved for closure of other intracardiac defects like ASD, VSD, and PDA have been utilized in an off-label fashion for transcatheter PVL closure. We most commonly use an Amplatzer VSD occluder and/or Amplatzer vascular plug for these defects.

- B. Procedure.** In order to deploy an occlusion device across a PVL, it is first necessary to cross the defect with a delivery catheter. Aortic PVLs are generally crossed in a retrograde fashion from the femoral artery. The mitral PVL may be crossed in retrograde fashion from the femoral artery via the left ventricle, in the antegrade fashion by advancing a catheter from the right atrium into the left atrium via transseptal puncture, or via direct transapical access. Similar to percutaneous VSD/VSR closure, creation of an AV loop is usually mandatory to form a supportive rail for the passage of equipment. In addition to the use of fluoroscopy, TEE, and ICE during the procedure, three-dimensional echocardiography has recently gained popularity for optimal anatomical characterization and guiding device placement.

In the retrograde approach for mitral PVL closure, a diagnostic catheter (such as an internal mammary artery or JR4 catheter) is placed in the left ventricle. Subsequently, a 0.035" × 260 cm floppy guidewire is used to cross the defect, and the catheter is advanced over this wire into the left atrium. To provide adequate support for the device delivery catheter, an AV loop is typically established during this procedure; transseptal puncture and a GooseNeck snare are used to externalize the wire to form a continuous AV loop. Subsequently, the closure device is introduced through a delivery catheter from the venous side, while withdrawing the guidewire ("chasing the wire"). The device is subsequently deployed across the PVL in a standard fashion.

In the antegrade approach, transseptal puncture is carried out first. We typically use an Agilis steerable catheter (St. Jude Medical) to navigate the left atrium and direct the wire toward the defect. The location of the transseptal puncture is also highly variable and is directed by the location of the PVL. Through this catheter, a wire (preferably a 0.035" guidewire) is advanced to cross the defect, and subsequently the catheter is advanced over this wire into the left ventricle. Subsequently, there is sequential delivery of increasingly supportive catheters (4F Bernstein, 6.5F JBI, Cook Medical) over more supportive wires (floppy guidewire, stiff guidewire, Amplatzer

ES) to facilitate the placement of the device delivery sheath into the left ventricle via the PVL defect. Again, creation of an AV loop by externalizing the wire at the femoral artery or via the LV apex is usually necessary. The PVL occluder device is deployed in a standard fashion.

- C. Complications.** Transcatheter mitral PVL closure has had variable success. The initial technical success has ranged between 60% and 90%, with up to a 40% reintervention rate. Immediate and delayed device-related complications have been described as a result of technical failure. The early technical failure happens due to device impingement on nearby critical structures, and the delayed technical failure happens as a result of device embolization. Persistent PVL and/or its associated sequelae (i.e., CHF and hemolytic anemia) may be encountered after PVL closure. Although no procedure-related deaths have been described in any series, rare instances of strokes, dysrhythmias, and cardiac perforation have been described.
- D. Outcomes.** Transcatheter PVL closure is one of the most challenging structural heart disease interventions. The long-term outcomes after transcatheter PVL closure largely depend upon surmounting the limitations imposed by the current nonspecific devices for PVL closure, as well as challenges in imaging of the area of interest. Over the long-term follow-up described in a few relatively large case series, resolution of hemolysis was reported in 60% to 83% of patients, improvement in CHF symptoms was reported in 50% to 100% of the patients, and repeat surgery was required in only 4% to 18% of the individuals. The incidence of long-term mortality has ranged from 25% to 30% over 3 to 36 months of follow-up across various studies.

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Transthoracic Echocardiography

- I. INTRODUCTION.** Transthoracic echocardiography is a reliable and versatile tool for the assessment of cardiac structure, function, and hemodynamics. It has advantages over other cardiovascular imaging modalities in that it is relatively inexpensive, does not incur radiation exposure to the patient, is noninvasive, displays live real-time images, and is widely available. Common indications and corresponding aims of the echocardiographic evaluation are listed in Table 67.1.
- II. BASIC PRINCIPLES OF ECHOCARDIOGRAPHY.** Sound waves consist of mechanical vibrations that produce alternating compressions and rarefactions of the medium through which they travel. **Ultrasound** consists of sound waves in the frequency range that is higher than what is audible by humans ($> 20,000$ Hz). All waves can be described by their frequency (f), wavelength (λ), velocity of propagation (v), and amplitude. The velocity of ultrasound in soft tissue (e.g., myocardium and blood) is 1,540 m/s. Frequency is defined by the number of cycles occurring per second (cycles/second or Hz) and wavelength is measured in meters (m). Velocity, frequency, and wavelength are described by the following relationship:

$$\text{Velocity} = \text{frequency} \times \text{wavelength} \text{ or } v = f \times \lambda$$

The typical adult echocardiographic examination uses a transducer with ultrasound frequency between 2.5 and 3.5 million Hertz (MHz). Based on the equation above, a 3-MHz transducer results in an ultrasound wavelength of approximately 0.50 mm. This has important implications since image resolution cannot be > 1 to 2 wavelengths (e.g., 1 mm with a 3-MHz transducer). In addition, the depth of penetration of the ultrasound wave is directly related to the wavelength, with shorter wavelengths penetrating a shorter distance. Therefore, higher frequency transducers result in the use of shorter wavelengths that improve image resolution but at the cost of reduced depth penetration.

Transducers use a piezoelectric crystal to generate and receive ultrasound waves. A piezoelectric substance has the property of changing its size and shape when an electric current is applied to it. An alternating electrical current will result in rapid expansions and compressions of the material and thus produce an ultrasound wave. The piezoelectric crystal also deforms in shape when an ultrasound wave strikes the material, resulting in the production of an electric current. The transducer, and the piezoelectric crystal, thus oscillates between a short burst of transmitting ultrasound waves, with a brief period of no ultrasound transmission when it awaits reception of the reflected signals.

Tissue harmonic imaging has become the standard imaging technique in many laboratories. It utilizes the principle that as ultrasound waves propagate through tissue, the waveform becomes altered by the tissue, with the generation of new waveforms of higher frequency but which are **multiples of the baseline fundamental frequency**. Setting the transducer to receive only harmonic sound waves that are multiples of the fundamental frequency improves image quality significantly. This image quality improvement is based

TABLE 67.1 Common Indications and Corresponding Aims of Echocardiographic Evaluation

Indications	Echocardiographic evaluation
Valvular heart disease	Valve morphology, regurgitation and/or stenosis severity and etiology, and ventricular size and function
Infective endocarditis	Vegetation, abscess, fistula, valvular function, and ventricular size and function
Coronary artery disease	Wall motion abnormalities, ventricular function, and mitral regurgitation/ventricular septal defect and other ischemic complications
Congestive heart failure	Systolic function, wall motion abnormalities, chamber size, valvular pathology, and diastolic function
Pericardial disease	Pericardial effusion, pericardial thickening \pm calcification, and RV size and function
Cardiac tamponade	Pericardial effusion; RA diastolic collapse; RV early diastolic collapse; respiratory variations in mitral, tricuspid pulmonary venous, and hepatic venous flow; and IVC size and respiratory variation
Ascending aortic pathology	Aneurysm, atheroma, dissection or intramural hematoma, and aortic valve pathology
Pulmonary hypertension	RV systolic pressure, RV and LV function, and tricuspid, pulmonary, and mitral valve pathology
Systemic hypertension	Interatrial shunt and respiratory effects on IVC diameter LV function, LV wall thickness, and evidence of aortic coarctation
Embolic disease	LA and LV thrombus, mitral valve pathology, aortic atheroma, LV function, and interatrial shunt
Arrhythmias	LA and LV thrombus, ventricular size and function, atrial dimensions, and mitral valve pathology
Syncope	LV outflow tract obstruction, aortic and mitral valve pathology, LV function, and congenital abnormalities
Cardiac trauma	Ascending aortic dissection, ascending aortic aneurysm, and cardiac tamponade
Congenital heart disease	Congenital anomaly and shunt calculation
Critical illness	LV function, valvular pathology, pericardial effusion/tamponade, right-to-left shunt, and volume status

IVC, inferior vena cava; LA, left atrial; LV, left ventricular; RA, right atrial; RV, right ventricular.

on the fact that weak signals, which tend to be artifacts, create almost no harmonics. In addition, shallow structures, such as the chest wall, generate weak harmonic signals, whereas at depths of 4 to 8 cm, where the heart is located, maximal harmonic frequencies develop. These phenomena result in fewer near-field artifacts and better endocardial definition. One limitation of harmonic imaging is that valve leaflets appear thicker—an artifact generated during image processing that appears to be related to the rapid motion of the leaflets.

The steps involved in creating a final ultrasound image are transmission and reception of waves, conversion to electrical signals, filtering, and extensive computer processing. The details of image processing, formation of artifacts, advanced physics, and technical aspects of echocardiography are beyond the scope of this chapter, but these are briefly discussed in Section VII.

Patient and probe positioning, electrocardiographic lead placement, and transducer selection are the first steps to beginning the echocardiographic examination.

- A. Patient and probe positioning.** The probe can be held with the right or left hand depending on the patient side that one chooses to scan from. For the parasternal and apical positions, the patient should be in the left lateral decubitus position, with the left arm extended behind the head, as this brings the heart into contact with the chest wall. The subcostal and suprasternal views require the patient to be in the supine position.
- B. Electrocardiographic lead placement.** The ECG allows identification of arrhythmias and timing of cardiac events during the echocardiographic examination, and it is used as a timing marker for digital recording of images. Typically, digital “clips” are set to record a predefined number of cardiac cycles (usually one but sometimes two), with timing based on the ECG. It is important that irregular beats be identified and excluded from the analysis. For example, a postectopic beat will falsely increase the two-dimensional (2D) assessment of ejection fraction (EF) and the Doppler assessment of transaortic gradient. In general, any Doppler index requires the average of at least three measurements. For patients in atrial fibrillation, 7 to 10 beats should be averaged. For patients with very high heart rates, or with a noisy electrocardiographic signal, the digital clips can be set to record for a predefined period of time (usually 2 seconds).
- C. Transducer selection.** The adult echocardiographic examination typically begins with a 2.5- to 3.5-MHz phased array transducer. Transducer frequency is important, as at higher frequencies spatial resolution improves but at the expense of reduced depth penetration. Higher frequency (3.0 to 5.0 MHz) transducers may be used in thin or pediatric patients or intraoperatively for epiaortic scanning. Therefore, for optimal 2D resolution, select the highest frequency transducer that will provide adequate far-field penetration.

With regard to transducer frequency for the Doppler examination, lower frequency transducers can record higher velocities (see Doppler equation later in the chapter). The Pedoff probe is a continuous-wave (CW), nonimaging probe (typical frequency being 1.8 MHz) used mainly to detect higher velocity profiles and confirm velocities obtained by other imaging methods.

III. IMAGING MODALITIES IN STANDARD ECHOCARDIOGRAMS

- A. M-mode.** Prior to 2D imaging, the echocardiogram was obtained when the transducer sent an ultrasound wave along a **single line** and then displayed the amplitude of reflected signal as well as the depth of that signal on an oscilloscope. This was called an A-mode echocardiography. When these line-of-sight ultrasound images were plotted with respect to time, “motion” mode, or M-mode, was produced. Despite the increasing emphasis on 2D imaging, the M-mode display remains a complementary element of the transthoracic examination. Its **high sampling rate** of approximately 1,800/s, compared with 30/s for 2D echocardiography, provides **excellent temporal resolution**, and thus it is very **useful in the timing of subtle cardiac events** that can be missed by the naked eye in 2D imaging. Rapidly moving structures such as the aortic valve, mitral valve, and endocardium have characteristic movements in M-mode. Deviations from these, such as diastolic fluttering of the mitral valve in aortic regurgitation (AR) and systolic aortic valve notching in dynamic left ventricular outflow tract (LVOT) obstruction, may be the only way to detect underlying dysfunction when they are not appreciated in other imaging modalities.

M-mode also has a great spatial resolution along the single line and can be used for precise size measurements such as ventricular dimensions in systole and diastole. The M-mode image is displayed like a graph, with **time on the x-axis and distance from the transducer on the y-axis**, with the structures closest to the transducer at the top of the image. In order to align the line of sight accurately, **2D imaging should be used to position the M-mode cursor** through the structures of interest.

- B. Two-dimensional imaging.** Two-dimensional imaging provides the **tomographic views** that are envisioned when one thinks of a transthoracic echocardiogram. It not only provides various 2D planes of cardiac structures but also acts as the platform that guides the M-mode and Doppler portions of the examination.

The 2D echocardiographic image is essentially the scan line from M-mode that, instead of having a fixed line of sight, is swept back and forth across an arc. After complex manipulation of the **data received by the transducer from the multiple scan lines**, a 2D tomographic image is generated for display.

Depending on the depth of the image, a finite amount of time is needed for each scan line to be sent and received by the transducer. As opposed to M-mode that has only one scan line and can provide over 2,000 frames/s, 2D echocardiographic imaging can utilize 128 scan lines but at the expense of a lower rate of 30 frames/s. Faster frame rates can be obtained by electronic manipulation using parallel processing on current ultrasound machines. Doppler overlay of the 2D image tends to slow down the frame rate. This **reduction in temporal resolution** reinforces the need for M-mode to complement 2D imaging in echocardiography, especially for rapidly moving structures and in precise timing of events.

- C. Doppler echocardiography.** The introduction of Doppler technique to echocardiography not only added new imaging capabilities but also transformed echocardiography into a modality that could provide **hemodynamic assessment** of the heart. Echocardiography has now become the preferred method, and in some cases the gold standard, over cardiac catheterization for certain hemodynamic assessments.

- 1. Doppler principles.** The Doppler principle states that sound frequency increases as the sound source moves toward the observer and decreases as the source moves away. The change in frequency between the transmitted sound and the reflected sound is termed the **Doppler shift**. This phenomenon is appreciated daily when an ambulance's siren becomes higher pitched, due to the increase in wave frequency, as it approaches the observer and then lower pitched once it has passed. This Doppler frequency shift directly relates to the velocity of the red blood cell by the following **Doppler equation**:

$$v = \frac{c(f_r - f_t)}{2f_t(\cos \theta)}$$

where v = velocity, f_r = frequency received, f_t = frequency transmitted, c = speed of sound in blood (1,540 m/s), and θ = angle between moving object and ultrasound beam.

The $\cos \theta$ in the Doppler equation makes the calculation of velocity depending on the angle between the beam and the moving structure (red blood cell). Echocardiography machines do not typically incorporate the angle for calculating the resultant velocity, and thus the goal is to have the angle between the ultrasound beam and the blood flow jet of interest to be as close to zero as possible ($\cos 0 = 1$). When this is not possible, the angle should be $< 20^\circ$, so that the true flow velocity is underestimated by $< 6\%$ ($\cos 20 = 0.94$). Adhering to this requirement sometimes mandates off-axis or unusual 2D images to align the Doppler ultrasound signal with desired target. Reference Doppler velocities in the adult examination are given in Table 67.2.

TABLE 67.2 Normal Echo Dimensions in Adults

Factor	Ref. range (cm)	Factor	Ref. range (cm)
(i) Parasternal long axis (M-mode or 2D)			
LV end-diastolic diameter	3.5–5.7	LV end-systolic diameter	2.3–4.0
Septal thickness (ED)	0.6–1.1	Posterior wall thickness (ED)	0.6–1.1
Aortic root (ED—M-mode)	2.0–3.7	Left atrium (ES)	1.9–4.0
RV end-diastolic diameter	1.9–3.8		
Aortic annulus (systole—2D)	1.4–2.6	Midascending (2D)	2.1–3.4
(ii) Four-chamber view			
LV volume (ED) (cm ³)	96–157	LV volume (ES) (cm ³)	33–68
Ejection fraction (%)	59 ± 6		
Left atrial area (cm ²)	< 20		
(iii) Doppler velocities			
Mitral E wave (< 50 y) (cm/s)	72 ± 14	Mitral E wave (> 50 y) (cm/s)	62 ± 14
Mitral A wave (< 50 y) (cm/s)	40 ± 10	Mitral A wave (> 50 y) (cm/s)	59 ± 14
Deceleration time (ms)	140–210		
Ascending aorta (m/s)	1.0–1.7	LV outflow tract (m/s)	0.7–1.1
Pulmonary artery (m/s)	0.5–1.3		
Pulmonary vein S wave (cm/s)	56 ± 13	Pulmonary vein D wave (cm/s)	44 ± 16
Pulmonary vein A reversal (cm/s)	32 ± 7		

ED, end-diastole; ES, end-systole; LV, left ventricular; RV, right ventricular.

2. **Spectral analysis** is the term used to describe the way in which pulsed-wave (PW) Doppler and CW Doppler are displayed. By convention, the horizontal axis reflects time and is placed in the middle of the screen with upward deflections representing frequency shifts toward the transducer and downward deflections for frequency shifts away from the transducer. The vertical axis represents the blood flow velocity (or frequency shifts), with the density of pixels on a gray scale reflecting the amplitude of the signal. The final result is that at each time-point the spectral analysis shows blood flow direction, velocity/frequency shift, and signal amplitude.

- a. **PW Doppler.** The purpose of PW Doppler mode is to measure the Doppler shift, and thus velocity, at a **specific location of interest within a small sample volume** (e.g., mitral inflow velocity at the mitral valve leaflet tips, systolic velocity at the LVOT, and blood flow within the pulmonary veins). In this mode, a **single crystal** sends short bursts of ultrasound waves at a

specific pulse repetition frequency (PRF) to a specific location, which are reflected from moving blood cells at this location and received by the same crystal. The maximal velocity that can be measured is limited by the time required to transmit and receive the ultrasound wave. This is called the **Nyquist limit** (one-half of the PRF). If a velocity greater than the Nyquist limit is measured, the signal appears as a wrap around the baseline, known as **signal aliasing**. Hence, the peak velocity is limited by the depth of the area of interest and also by the transducer frequency (inverse relationship according to the Doppler equation; see previous text). **PW Doppler has excellent spatial/depth resolution, but it has limited capacity to measure high velocities due to the Nyquist limit.** It is, therefore, used primarily to measure low-velocity flow (< 2 m/s) at specific sites in the heart.

- b. **CW Doppler.** CW Doppler employs **two crystals, one continuously sending ultrasound waves and the other continuously receiving the waves.** It measures Doppler shift **along the entire beam**, rather than at a specific location. Unlike PW Doppler, CW Doppler measures the **maximal velocity along the entire ultrasound beam** but it does not localize the precise position of that peak velocity. However, this is often apparent anatomically or can be deduced using PW Doppler or color flow Doppler. **In general, CW Doppler is used to assess high-velocity flow and PW Doppler is used to measure low-velocity flow in specific areas.** Clinical applications of PW versus CW Doppler are listed in Table 67.3.
- c. **Color flow imaging.** Although spectral (pulsed-wave and continuous-wave) Doppler imaging is superior for accurate measurement of specific intracardiac blood flow velocities, the best way to visualize the overall pattern of intracardiac blood flow is with color flow imaging. Color flow Doppler is based on the principle of PW Doppler, with multiple sampling volumes at

TABLE 67.3

Differences and Uses of Pulsed-Wave Doppler and Continuous-Wave Doppler

Factor	Pulsed wave	Continuous wave
Transducer crystal	Same transmitting and receiving	Different transmitting and receiving
Spatial resolution	Excellent—localizes to precise point	Poor—may be anywhere along the entire beam
Ability to measure high velocity (> 2 m/s)	No (limited by Nyquist)	Excellent
Uses	Mitral inflow	Gradients in aortic stenosis
	Pulmonary venous flow and LVOT flow	Gradient and pressure halftime in mitral stenosis
	Hepatic vein flow	Peak velocity in mitral regurgitation and measurement of dp/dt
	Tricuspid inflow	
		TR velocity—estimate RV systolic pressure

LVOT, left ventricular outflow tract; RV, right ventricular; TR, tricuspid regurgitation.

varying depths along a single scan line. A full-color flow map is generated by combining multiple scan lines along the areas of interest. To accurately estimate the velocity along a given scan line, the instrument compares the Doppler shift changes from several successive pulses (typically eight), and this is known as the **burst length**. Where Doppler shifts are detected, color pixels are displayed at that location with the different colors representing the different degrees of Doppler shift based on a predetermined color spectrum. Tradition has set **blood velocity toward the transducer as shades of red and blood flow away as shades of blue (Blue Away)**.

Since this modality uses properties based on PW Doppler technology, color flow Doppler has limitations similar to those of PW Doppler for velocity determination. When the flow velocity is higher than the Nyquist limit (indicated on the color map), color aliasing occurs (depicted as color reversal, red to blue or blue to red transition). The fact that color aliasing occurs can actually provide important hemodynamic information, such as identification of flow acceleration or calculation of the proximal isovelocity surface area (PISA), which is discussed in Section VI.C.6.

- d. **Tissue Doppler imaging (TDI).** TDI is based on adjusting standard Doppler to focus primarily on the low-velocity, high-amplitude **motion of the myocardium** (usually < 20 cm/s) instead of the high-velocity, low-amplitude motion of red blood cells. Decreasing the filters (which normally eliminates low-velocity signals) and the Doppler transmit gain (which excludes the low-amplitude blood signals) results in the Doppler focusing primarily on myocardial motion. TDI can be displayed as either PW Doppler, typically at one aspect of the mitral annulus (usually septal or lateral) or by color flow TDI mapping of the entire myocardial area of interest (Fig. 67.1). TDI has primarily been used as an adjunct for the evaluation of left ventricular (LV) diastolic function, where the mitral annular TDI pattern shows a systolic (S) wave toward the transducer and two diastolic waves away from the transducer (corresponding to early relaxation and late atrial diastolic myocardial motion, labeled as E' and A') (Fig. 67.2 and Table 67.4). With worsening diastolic function, E' velocity decreases and is directly proportional to the rate of relaxation. TDI annular velocities decrease with age and may be affected by a myocardial infarction in the region adjacent to the annulus or surgery of the mitral valve. Therefore, TDI can be used to help differentiate

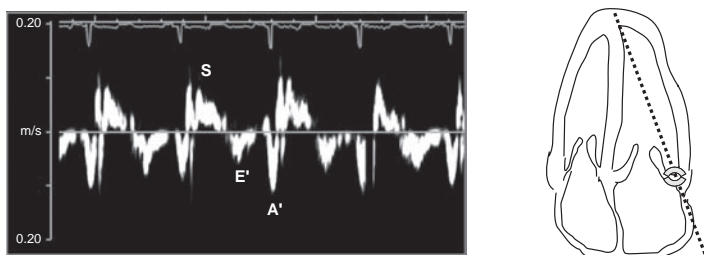


FIGURE 67.1 Tissue Doppler imaging (TDI) for diastolic function recorded from the apical four-chamber window using a 2-mm sample volume positioned in the lateral wall 1 cm from the mitral annulus. The TDI signal is toward the transducer in systole (S) as the myocardium moves toward the apex. In diastole, the myocardial velocity is directed away from the transducer first with early diastolic filling (E') and then with atrial contraction (A').

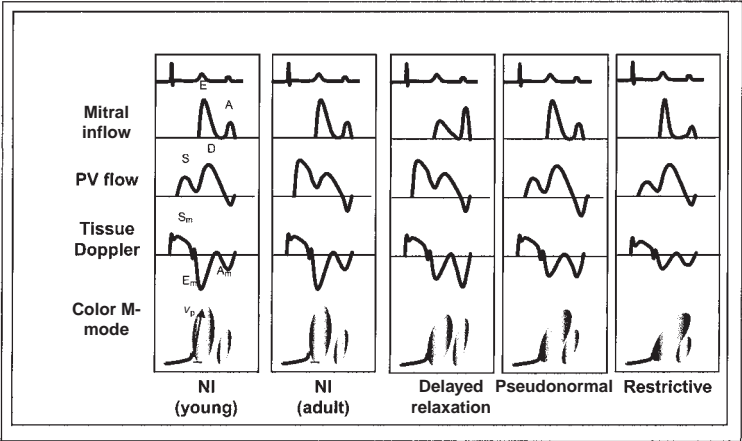


FIGURE 67.2 Diastolic function/dysfunction staging. PV, pulmonary vein; Tissue Doppler: mitral annular velocity by Tissue Doppler; NI, normal; S, systolic; D, diastolic; S_m , systolic annular velocity; E_m , early diastolic annular velocity (E'); A_m , atrial annular velocity (A'); V_p , velocity of propagation; E, early mitral inflow velocity; A, atrial kick mitral inflow velocity.

a normal mitral inflow pattern (normal E') from a pseudonormal filling pattern (reduced E') (Fig. 67.2 and Table 67.4). TDI can also be used to assess LV filling pressures, myocardial deformation, and ventricular dyssynchrony.

D. Color M-mode (CMM). This technique, whereby color flow Doppler is imposed on an M-mode image, permits excellent spatiotemporal distribution of velocity (color) data, although it is limited to the defined scan line. It is a valuable adjunct in the timing of cardiac events, which may not be readily appreciated by 2D and color flow imaging alone. Its primary use has been in evaluating diastolic filling pattern where the LV inflow CMM pattern typically has two appreciable waves, the first demonstrating the early passive filling wave and the second later wave resulting from atrial contraction (Fig. 67.2). The slope of the early filling wave (velocity of propagation, V_p) is primarily

TABLE 67.4 Diastolic Function/Dysfunction Staging						
	Normal young	Normal adult	Normal elderly	Delayed relaxation	Pseudonormal filling	Restrictive filling
Stage	Normal	Normal	Normal	I	II	III
E/A ratio	> 1 (often > 2)	> 1	< 1	< 1	1–2	> 2
DT (ms)	< 220	< 220	> 220	> 220	150–200	< 150
S/D ratio	< 1	≥ 1	> 1	> 1	< 1	< 1
Ar (cm/s)	< 35	< 35	< 35	< 35	> 35	> 25
V_p (cm/s)	> 55	> 55	< 55	< 55	< 45	< 45
E' (cm/s) (E annulus)	> 10	> 8	< 8	< 8	< 8	< 8

dependent on the rate of relaxation and is reduced with delayed relaxation. It is useful for differentiating a normal mitral inflow pattern (normal V_p) from a pseudonormal filling pattern (where impaired relaxation results in delayed flow propagation into the left ventricle, slower V_p) (Fig. 67.2 and Table 67.4).

Other uses of CMM are the accurate measurement of AR jet diameter in the LVOT in the parasternal views and, with its superior temporal resolution, detection of diastolic mitral regurgitation (MR), which may be seen in certain conditions (severe acute AR, advanced diastolic dysfunction, and complete heart block).

IV. TOMOGRAPHIC VIEWS AND CARDIAC ANATOMY. Most echocardiography laboratories have similar protocols for acquisition of a complete echocardiogram with only slight differences. Each echocardiographic view is labeled first by the transducer position (parasternal, apical, subcostal, and suprasternal) followed by the tomographic view of the heart (long axis, short axis, four chamber, and two chamber). To acquire these different views, the transducer is placed on different parts of the body and adjusted with rotation and angulation to optimize the final image. Standard imaging planes are illustrated in Figures 67.3 to 67.8; see Table 67.5 for standard examination protocol and Table 67.6 for useful examination tips.

A. Parasternal. The parasternal position is typically obtained by placing the transducer at the left of the sternal border in the third or fourth intercostal space. The optimal position for the patient is usually the left lateral decubitus position, but sometimes some hybrid between the steep left lateral and supine position is required to optimize the view. This position allows imaging of the long axis as well as the short axis of the heart.

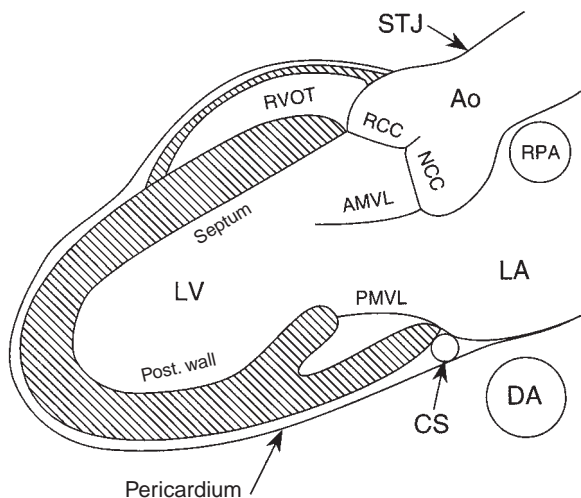


FIGURE 67.3 Schematic diagram of the parasternal long-axis view in diastole. AMVL, anterior mitral valve leaflet; Ao, aorta; CS, coronary sinus; DA, descending aorta; LA, left atrium; LV, left ventricle; NCC, noncoronary cusp; PMVL, posterior mitral valve leaflet; post. wall, posterior wall; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; STJ, sinotubular junction. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

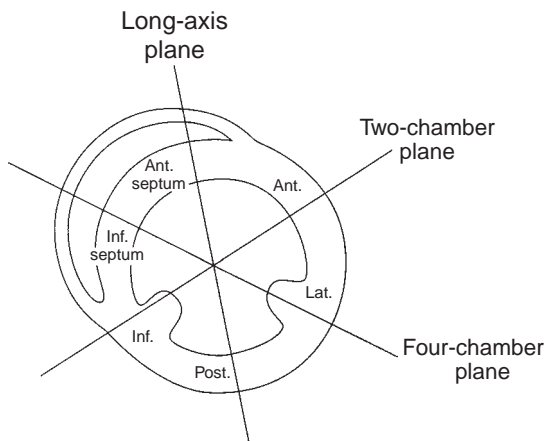


FIGURE 67.4 Schematic diagram of the parasternal short-axis view at the level of papillary muscles. Ant. septum, anterior septum; Ant., anterior wall; Inf. septum, inferior septum; Inf., inferior wall; Lat., lateral wall; Post., posterior wall. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

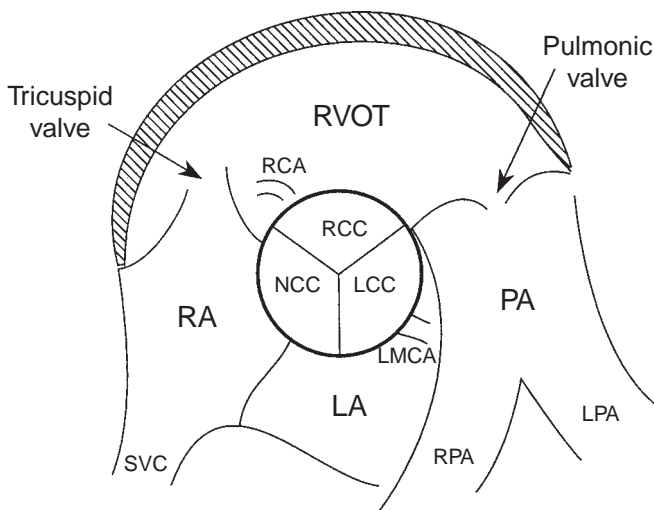


FIGURE 67.5 Schematic diagram of the parasternal short-axis view at the aortic valve level. LA, left atrium; LCC, left coronary cusp; LPA, left pulmonary artery; NCC, noncoronary cusp; PA, pulmonary artery; RA, right atrium; RCA, right coronary artery; RCC, right coronary cusp; RPA, right pulmonary artery; RVOT, right ventricular outflow tract; SVC, superior vena cava; LMCA: left main coronary artery. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

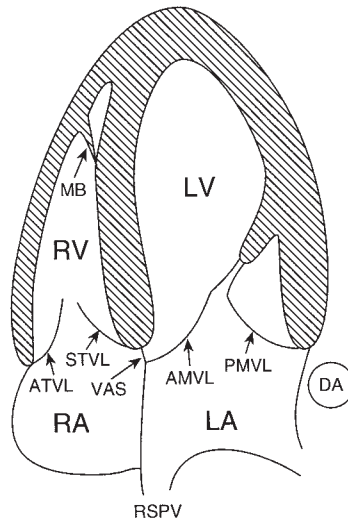


FIGURE 67.6 Schematic diagram of the apical four-chamber view. AMVL, anterior mitral valve leaflet; ATVL, anterior tricuspid valve leaflet; DA, descending aorta; PMVL, posterior mitral valve leaflet; LA, left atrium; LV, left ventricle; MB, moderator band; RA, right atrium; RV, right ventricle; STVL, septal tricuspid valve leaflet. VAS, ventriculoatrial septum (where communication from LV to RA may occur); RSPV, right superior pulmonary vein. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

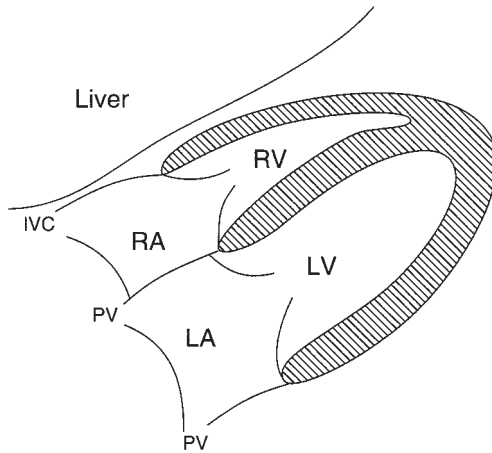


FIGURE 67.7 Schematic diagram of the four-chamber view from the subcostal approach. IVC, inferior vena cava; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; PV, pulmonary vein. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995: 21–64, with permission.

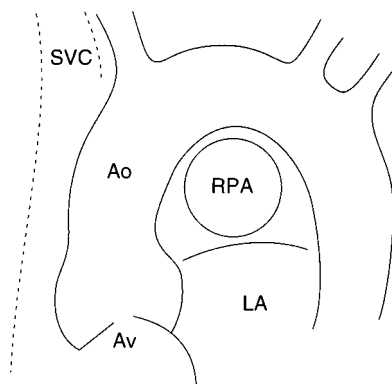


FIGURE 67.8 Schematic diagram of the aorta and right pulmonary artery from the suprasternal notch window. Ao, aorta; AV, aortic valve; LA, left atrium; RPA, right pulmonary artery; SVC, superior vena cava. From Otto CM, Pearlman AS. *Otto and Pearlman's Textbook of Clinical Echocardiography*. Philadelphia, PA: WB Saunders; 1995:21–64, with permission.

TABLE 67.5 Standard Transthoracic Examination

1. PLAX

- Position transducer in third or fourth intercostal space parasternally (ridge toward right shoulder)
- Color Doppler—mitral and aortic valve flow and interventricular septum (in cases of ventricular septal defect)
- M-mode—three levels (below mitral leaflets, midmitral leaflets, and aortic valve)
- Move up an intercostal space to get better view of ascending aorta
- Tilt transducer inferomedially to assess RV inflow. Color Doppler to assess tricuspid regurgitation and CW Doppler to estimate RVSP

2. PSAX

- Rotate transducer 90° clockwise from PLAX and tilt transducer from superior to inferior (LV apex view, mid-LV view, mitral valve view, and aortic valve level)
- Color Doppler at mitral valve level (localize mitral regurgitation if present)
- Color Doppler at aortic valve level (localize aortic regurgitation and assess flow in RVOT/pulmonic valve and tricuspid valve)
- PW Doppler—RVOT (level of pulmonic valve annulus)
- CW Doppler—RVOT/pulmonic valve and tricuspid valve (estimate RVSP)

3. A4C

- Transducer at apex—ridge toward left (move laterally and inferiorly if necessary to get true apex)
- Color Doppler—mitral flow and tricuspid flow
- Measure PISA if mitral regurgitation (zoom, decrease Nyquist, and measure radius)
- PW Doppler—mitral inflow—position at level of mitral leaflet tips (gate 1–2 mm)

TABLE 67.5 **Standard Transthoracic Examination (Continued)**

- PW Doppler—PV (usually right upper PV)—1–2 cm into vein (gate 3–4 mm)
- CW Doppler—across mitral valve (stenosis and/or regurgitation and to calculate PISA)
- CW Doppler—tricuspid flow (estimate RV systolic pressure)
- Tilt transducer anteriorly to obtain “five-chamber view,” i.e., open up aortic valve/LVOT
- Color Doppler—LVOT/aortic valve
- PW Doppler—LVOT—at the level of the aortic annulus
- CW Doppler—LVOT/aortic valve
- Tilting transducer posteriorly will bring the coronary sinus in view (along AV junction, emptying into right atrium)

4. A2C

- Rotate transducer ~60–90° anticlockwise
- Tilt posteriorly and rotate clockwise to open out descending aorta

5. Apical long axis (apical three chamber)

- Rotate transducer further 30–45° anticlockwise
- Color Doppler—LVOT/aortic valve
- Recheck CW Doppler across aortic valve if evaluating for aortic stenosis

6. Subcostal view—patient supine and legs bent at knees

- Subxiphoid, midline, tilt anteriorly under sternum with groove toward patients left for four-chamber view
- Color Doppler across interatrial septum to check for a PFO or ASD
- Rotate transducer 90° from four-chamber view until groove is pointing anterosuperiorly
- Same views as PSAX except rotated 90° clockwise
- Sweep from left to right to get apical, midventricular, and aortic valve levels
- IVC should be visualized when scan plane is directed toward the right midclavicular region with some counterclockwise rotation to open out long axis of IVC
- Color Doppler—IVC flow
- PW of hepatic veins (may need to angle posteriorly)

7. Suprasternal view—patient supine and head tilted backward

- Transducer in suprasternal notch, with groove toward left (rotate to about 1 o'clock), parallel to trachea
- Color Doppler in arch and upper descending aortas (especially if suspected coarctation)
- PW Doppler in upper descending aorta (if assessing aortic regurgitation severity)

8. Pedoff probe

- Especially for checking maximal aortic valve gradient in aortic stenosis
- Apical position
- Right upper sternal border (aortic stenosis)

A4C, apical four chamber; A2C, apical two chamber; AV, atrioventricular; ASD, atrial septal defect; CW, continuous wave; IVC, inferior vena cava; LV, left ventricular; LVOT, left ventricular outflow tract; PLAX, parasternal long axis; PSAX, parasternal short axis; PFO, patent foramen ovale; PW, pulsed wave; PV, pulmonary vein; RV, right ventricular; RVOT, right ventricular outflow tract, RVSP, right ventricular systolic pressure.

TABLE 67.6 Tips for Transthoracic Two-Dimensional Examination

1. **Optimize patient position** (left lateral with left hand above head) and **environment** (darkened room).
2. Ensure imaging in **harmonics** mode.
3. Consider **contrast** to improve endocardial delineation for technically difficult studies.
4. When parasternal and apical images are limited (body habitus, surgical drains, dressings, etc.), the **subcostal window** may be the only accessible window.
5. Consider **off-axis views** to enhance visualization of specific structures.
6. Obtain images at **end of expiration**, as the heart is closer to the transducer.
7. **Avoid foreshortening LV apex** (especially in A2C)—true apex may be more inferior and lateral than expected.
8. If there is a **concern of LV thrombus**, zoom and check with low-velocity color Doppler to ensure flow throughout. Consider contrast if unclear.
9. If an object is suspicious for an artifact, reassess in other imaging planes.
10. **M-mode** can be useful especially for the accurate timing of cardiac events (especially RV or RA collapse in the setting of possible tamponade or assessment of possible systolic anterior motion of the mitral valve).
11. Adjust transducer **frequency** to maximum that permits adequate far-field penetration/depth.
12. Set **time gain compensation** in the midrange with lower gain in the near field and higher settings in the far field to compensate for attenuation of the beam with increasing distance from transducer.
13. Use the least amount of **depth** that adequately shows the entire area of interest.
14. Adjust the **transmit gain/output** to optimize image brightness/quality—too low, everything appears black, too high results in a “white-out.” Initially set it to high and then adjust downward.
15. Adjust the **“compress”/dynamic range**. Decrease if image quality is poor to produce high-quality contrast images. Increasing it will “soften” images. Typically as compress is increased, the transmit gain should be decreased to maximize the spectrum of the gray scale.
16. Adjust the **focus** (focal zone) to include the area of interest, as the beam is narrowest (improves image resolution) within this area, especially when imaging near-field structures (e.g., looking for an apical LV thrombus from the apical windows).
17. Set the **persistence** to low.

LV, left ventricular; A2C, apical two chamber; RA, right atrial; RV, right ventricular.

1. **Parasternal long axis (PLAX).** The PLAX tomographic view is traditionally the first view of a standard transthoracic echocardiogram. The ultrasound beam is lined up between the patient's right shoulder and the left flank. The right ventricular outflow tract (RVOT) is located at the top of the image, the aorta to the right, the inferolateral (or posterior) wall on the bottom, and the cardiac apex on the left. The anteroseptum is visualized between the RVOT and the LV cavity. Therefore, the PLAX view of the heart is similar to the sagittal view of the left ventricle if viewed from the patient's left side in the supine position. Tilting

the transducer's tail toward the left shoulder with slight clockwise rotation aims the ultrasound beam inferomedially and brings the right ventricular inflow into view. This is good for obtaining the tricuspid regurgitation (TR) velocity as well as viewing the tricuspid valve, RV apex, and the right atrium.

2. **Parasternal short axis (PSAX).** While the transducer is still in the parasternal position, rotating the transducer clockwise to approximately 90° displays the heart in the short axis. The ultrasound beam in this case is roughly from the left shoulder to the right flank. Using different degrees of transducer tilting, and occasionally moving up or down an intercostal space, results in four traditional views of the heart. On tilting from superior to inferior, the views obtained are aortic valve–RV outflow, mitral valve level, midventricle at the papillary muscles, and the LV apex. The images appear as if viewing the heart from the apex and looking through to the base; therefore, the septum is on the left, lateral wall on the right, the anterior and anteroseptal walls at the top, and the posterior–inferior walls on the bottom of the screen.
- B. Apical.** The apical position is obtained with the patient still in the left lateral position and the probe placed at the apical impulse. This position obtains images in the long axis of the heart.
1. **Apical four chamber (A4C).** The A4C view is obtained with the ultrasound beam transecting the thorax in a superior–inferior fashion. Most institutions orient the transducer to place the left ventricle on the right side of the screen and the right ventricle on the left side. The apex is at the top of the image and the atria at the bottom regardless of the orientation. The inferoseptal and anterolateral walls as well as apex of the left ventricle can be assessed in this view.
 2. **Apical five chamber (A5C).** A slight rotation of the transducer introduces a fifth “chamber” in view, the proximal aorta. The aortic valve and LVOT also appear. This view allows for hemodynamic assessment of the LVOT and aortic valve as well as an additional view for aortic valve pathology.
 3. **Apical two chamber (A2C).** Further rotation, 90° counterclockwise from the A4C view, obtains the A2C view. In addition to the left atrium, the LV anterior wall, inferior wall, apex, and mitral valve are also well visualized.
 4. **Apical three chamber (A3C).** A slightly more counterclockwise rotation (approximately 30°) brings the aorta back into view, resulting in the A3C, or apical long-axis, view. This essentially has the same anatomical structures as those in the PLAX view with a different orientation. The apex is better visualized and the RVOT usually drops out of the image. Additional information on mitral and aortic valve hemodynamics can be obtained in this view, which is not ideally obtained in the PLAX view.
- C. Subcostal.** In a standard transthoracic examination, the subcostal view provides additional views of the ventricles, atria, and atrial septum that had been acquired in earlier portions of the examination (but now with a different orientation). However, in some patients with poor parasternal and apical views (e.g., hyperinflated lungs), the subcostal view may be the only way to obtain images of the heart since the parasternal and apical locations may have poor windows.
- The subcostal position is located caudal to the xiphoid process, with the patient in the supine position. The transducer is placed in the midline nearly parallel to the long axis of the patient's body so that the ultrasound beam slices toward the spine. This shows the right ventricle at the top right, the left ventricle at the bottom right, and their respective atria on the left. Clockwise rotation along with inferior tilting brings the inferior vena cava (IVC) and hepatic veins into view, which are used for right-sided hemodynamic assessments.
- In patients with very poor parasternal and apical windows, modified views from the subcostal position can be incorporated in the examination to gather the images from a different perspective.

- D. Suprasternal.** Placing the transducer in the suprasternal notch and pointing inferiorly can assess the ascending aorta, aortic arch, and descending aorta. Hemodynamics from this position can better characterize AR as well as the presence of coarctation.

V. ADVANCED ECHOCARDIOGRAPHIC TECHNIQUES

- A. Contrast echocardiography.** Contrast echocardiography is performed by injecting either **agitated saline** or one of the **commercially available contrast agents** into an arm vein. The choice of agitated saline versus commercial contrast agents depends on whether the goal is to visualize the right atrium and ventricle versus the left ventricle and myocardium. Both are microbubbles that reflect ultrasound waves and opacify intracardiac chambers. The size of the microbubbles relative to the pulmonary capillary diameter determines whether they cross to the left side of the heart or get trapped in the pulmonary circulation.

Agitated saline is sterile saline (preferably mixed with some blood), combined with a small quantity of air, which has been exchanged rapidly using a three-way stopcock between two syringes to create small bubbles. These relatively large (and unstable) bubbles are caught in the lung and do not routinely appear in the left side of the heart. However, after the bubbles are seen within the right atrium, their appearance in the **left atrium within three beats** of the cardiac cycle suggests a right-to-left **intracardiac shunt**—typically from a small patent foramen ovale. Contrast may appear in the **left atrium more than four beats** after it is seen in the right atrium, and this more likely signifies an **intrapulmonary shunt** rather than an intracardiac shunt. There is a small risk of embolic complications in the use of agitated saline. Care should be taken to avoid injecting larger air bubbles by inspecting the syringe closely prior to injection and ensuring that the bubbles are very small. Additionally, injecting contrast in a known large shunt should be avoided.

Modern commercial contrast agents consist of either an albumin-based shell containing perfluorocarbon gas (Optison) or a synthetic phospholipid shell containing perfluoropropane gas (Definity). These **microbubbles are much smaller** (the size of a red blood cell) and more stable; therefore, they can **cross the pulmonary capillaries and appear on the left side of the heart, where they opacify the LV cavity. Their primary uses are to improve endocardial definition** and to clarify the presence/absence of a suspected LV thrombus/mass. Ultrasound waves, especially those of higher power, destroy microbubbles; therefore, for optimal contrast imaging, it is important to reduce the mechanical index (the output of the machine), typically to 0.4 to 0.6.

Contrast also enhances Doppler signals, and agitated saline can be useful to augment the signal from TR to better estimate peak right ventricular systolic function (RVSP), whereas commercial microbubble products (Optison and Definity) can be used to enhance the Doppler envelope in patients with aortic stenosis when the image quality is suboptimal.

Contrast echocardiography was the subject of a black box warning from the FDA because of concerns of significant adverse events in patients who received it. More recent data suggest that adverse events following contrast injection are no more common than in those in whom it is not used when appropriate adjustment for severity of illness is made. Nevertheless, the FDA has recommended that patients with pulmonary hypertension or unstable cardiac conditions such as recent myocardial infarction, unstable angina, decompensated heart failure, ventricular arrhythmia, or respiratory failure should be monitored closely for at least 30 minutes after its use. It is contraindicated when a fixed or even transient right-to-left shunt is present or with documented allergy to its components such as blood products or albumin in the case of Optison.

- B. Three-dimensional (3D) echocardiography** is now emerging as a realistic imaging modality with improving image quality on newer generation 3D machines. Images are obtained using a transducer that transmits and receives data simultaneously in a 3D volume. Either real-time 3D images or biplane (orthogonal) simultaneous 2D images can be obtained. The 3D data set can then be manipulated using different software packages to assess function and anatomy. It is of particular benefit for the localization of valvular abnormalities (especially for the complex 3D mitral valve structure), accurate LV volume calculation, guiding surgical interventions (e.g., mitral valve repair), and complex congenital heart disease. Three-dimensional echocardiography allows for a better assessment of the right ventricle, which has a complicated geometry that is sometimes difficult to assess using 2D echocardiography. Three-dimensional color flow imaging allows for a comprehensive assessment of vena contracta and areas of flow convergence (PISA), which can improve the quantification of valvular regurgitation. It has been documented to allow for a more rapid evaluation of mitral valve area (MVA) in mitral stenosis as compared with conventional 2D planimetry. With the present technology, image resolution remains inferior to 2D imaging.
- C. Myocardial mechanics—tissue strain, strain rate imaging, and speckle tracking.** Strain rate imaging allows for the estimation of regional myocardial deformation and, therefore, function. **Tissue strain, a dimensionless entity, is a measure of the relative deformation of tissue.** Myocardial deformation in a segment of interest is assessed with reference to the adjacent segment, avoiding errors introduced by translational motion and tethering. **Strain rate is the rate of the deformation between two adjacent points of interest along a scan line and is expressed in seconds.** A strain rate curve can be derived by analyzing many adjacent segments along a scan line. Doppler techniques for assessing strain are not always ideal due to angle dependence, signal noise, and the need for a high frame rate. Doppler-independent techniques such as **speckle tracking** use ultrasonic reflectors (speckles) within tissues that can be followed from frame to frame through the cardiac cycle. This method can be used to assess the radial deformation and torsion of the ventricle. Strain rate is a relatively preload-independent measure of regional myocardial function. Clinical applications include assessment of myocardial ischemia, viability, diastolic function, subclinical LV dysfunction in valve disease, and cardiac involvement in systemic diseases such as diabetes or amyloidosis.
- D. Dyssynchrony.** Dyssynchrony occurs when different areas of the ventricles contract in an irregular pattern spatially and temporally. It is primarily seen in patients with impaired systolic function and electrophysiologic conduction delays. M-mode, 2D imaging, color Doppler, and tissue Doppler have all been employed to assess the amount of dyssynchrony but no consensus exists on the optimal approach to evaluate ventricular dyssynchrony (see Chapter 56). Some useful measures include the following:
1. A difference in the time to peak velocity of > 65 milliseconds between opposing walls (basal segments in four-chamber, two-chamber, and three-chamber views yielding a total of six segments) using pulsed tissue Doppler.
 2. A difference of 40 milliseconds in the interval from the QRS complex to the onset of flow in the RVOT versus the LVOT using pulsed tissue Doppler.
 3. Using M-mode or speckle tracking, a difference of 130 milliseconds in the septal to posterior wall delay.
- After the implantation of a resynchronization device, Doppler echocardiography is used for the optimization of programmed timing.

VI. SPECIAL TOPICS

- A. Systolic function.** Two-dimensional imaging is currently the primary echocardiographic means of determining systolic function of the heart. The most utilized

measurement is the EF. In the past, a common way of determining the EF was based on estimation by visual inspection. Recently, echocardiographic societies have recommended using standardized objective methods to minimize interobserver differences. LV volume is best measured using the modified Simpson's method (disk summation method). This involves tracing the LV area from two orthogonal views (typically A4C and A2C) and dividing the left ventricle into a number of cylinders of equal height. Total ventricular volume is calculated by adding up all the volumetric cylinders. All modern machines and digital echo reading systems have integrated software to create and combine the volume data after simply tracing the LV areas in both apical views. Based on the volumes measured in diastole and systole using this method, stroke volume (SV) and EF can be estimated from volume data obtained by **Simpson's method**:

Stroke volume (SV) = end-diastolic volume (EDV) – end-systolic volume (ESV)

$$EF = SV/EDV \times 100\%$$

$$EF = EDV - ESV/EDV \times 100\%$$

Newer semiautomated methods in 3D echocardiography using full matrix-array transducers give accurate, reproducible assessments of LV volume and EF that are superior to 2D methods when magnetic resonance imaging is used as the gold standard.

Finally, newer methods of assessing systolic function are becoming important. For example, LV torsion is a newer index for assessing LV systolic function that uses speckle tracking. The difference between the clockwise rotation of the base of the heart and the counterclockwise rotation of the apex of the heart (approximately 12°) can be evaluated using speckle tracking. Global strain also appears to be a robust parameter for assessment of LV function. Normally, LV peak systolic strain is negative and averages to $-18.6 \pm 0.1\%$.

In addition to the assessment of EF for the evaluation of systolic function, an assessment of regional wall motion and thickness is crucial in understanding the mechanism of disease. This is based on the fact that certain cardiac disease processes cause nonuniform abnormalities (coronary artery disease and sarcoidosis) and others cause global insults (hypertension and familial cardiomyopathy). For example, an EF of 35% that has a thin and akinetic anterior and anteroseptal wall would suggest an old transmural myocardial infarction due to occlusion of the left anterior descending artery. However, an EF of 35% with no regional wall abnormalities and thick myocardial walls could suggest amyloidosis or hypertension as the cause of the systolic dysfunction. Strain technology allows the display of regional variation in this modality that may be useful in understanding the regional manifestations of systolic dysfunction. For instance, in amyloidosis, strain is often preserved at the apex, but it is diminished in other areas of the heart.

- B. Diastolic function.** Doppler echocardiography remains the primary modality for assessing LV diastolic function, primarily by integrating information obtained from PW Doppler of mitral inflow and pulmonary venous flow combined with 2D assessment of left atrial size. Addition of CMM and TDI modalities can help optimize the assessment of degree of diastolic dysfunction, and combined mitral inflow/CMM (E/V_p) and mitral inflow/TDI (E/E') indices can be used to estimate LV filling pressures.

Traditionally, diastolic function was determined solely based on the assessment of mitral inflow pattern; however, with worsening diastolic function, a “pseudonormal” pattern appears (due to the opposing effects of delayed LV relaxation and elevated LV filling pressures), and this is indistinguishable from a normal diastolic filling pattern. Pulmonary venous flow can help differentiate these. Conventionally, the normal antegrade S/D pattern ($S > D$) should be reversed ($S < D$) in patients with pseudonormal LV diastolic filling, with an

increased retrograde atrial reversal velocity. However, optimal pulmonary venous flow images can be difficult to obtain, and flow patterns can be affected by other factors, including rhythm (atrial fibrillation) and valvular dysfunction (MR). Both CMM (delayed V_p) and TDI (reduced E') are useful to help confirm a pseudonormal filling pattern. An additional important key factor in assessing LV diastolic function is left atrial volume indexed to body surface area, which is invariably increased with worsening diastolic function. Significant diastolic dysfunction is unlikely to exist with a normal left atrial volume index. Accurate assessment of diastolic function not only is important for diagnosis of patients with primarily LV diastolic heart failure but is also of major prognostic importance for patients with systolic heart failure.

C. Hemodynamics

1. **Transvalvular pressure gradient.** The **Bernoulli equation** allows measurement of relative pressure differences across valves, shunts, or the LVOT. In its complete form, the Bernoulli equation is too complex for routine clinical use, as it incorporates three main components, namely, convective acceleration, inertial term (flow acceleration), and viscous friction. In many clinical situations, the latter two components can be ignored, leaving the flow gradient across an orifice to be derived from the convective acceleration term alone:

$$\Delta P = 4 \times (V_2^2 - V_1^2)$$

where V_2 is the velocity distal to an obstruction and V_1 is the velocity proximal to an obstruction.

The flow proximal to a narrowed orifice (V_1) is much lower than the peak flow velocity (V_2) and can be frequently ignored, leaving a **simplified Bernoulli equation**:

$$\Delta P = 4 V^2$$

The simplified Bernoulli equation is unreliable

- a. when V_1 is > 1 m/s, which occurs in serial lesions (subvalvular and valvular stenoses) and mixed stenosis with regurgitation.
- b. when viscous resistance becomes significant in the evaluation of long stenoses (e.g., coarctation or a tunnel-like ventricular septal defect).
- c. when the inertial term (flow acceleration) is not negligible (flow through normal valves).

It is important to realize that in aortic stenosis the Bernoulli equation represents the **maximal instantaneous gradient** across the valve, which is always higher than the customary peak-to-peak gradient measured in the catheterization laboratory since the LV systolic peak and aortic peak pressures do not occur at the same time and therefore are not instantaneous.

The flow within the heart is pulsatile; hence, mean gradients are an important measure and are obtained by integrating the velocity profile over the ejection time. This can be readily obtained with the software available on all modern echocardiography machines by simply tracing the area of the velocity profile. The mean pressure gradient is then derived from the mean velocity data using the Bernoulli equation.

2. Intracardiac pressure measurement

- a. **Estimated right atrial (RA) pressure** can be derived from the size of the IVC and its response to changes in respiration or a sniff (Table 67.7). Using a dilated IVC to assess elevated RA pressures is not accurate in mechanically ventilated patients; however, a small IVC of size < 1.2 cm in a mechanically ventilated patient is 100% specific for an RA pressure < 10 mm Hg.
- b. **Pulmonary artery systolic pressure (PASP)** is estimated from the TR peak velocity. Provided that there is no tricuspid valve obstruction, peak

TABLE 67.7 Estimation of Right Atrial Pressure

IVC	Change with respiration/sniff	Est. RA pressure (mm Hg)
Normal (< 1.7 cm)	Decrease > 50%	0–5
Dilated (> 1.7 cm)	Decrease > 50%	6–10
Dilated (> 1.7 cm)	Decrease < 50%	10–15
Dilated (> 1.7 cm)	No change	> 15

IVC, inferior vena cava; RA, right atrial.

TR velocity will depend on the pressure gradient between the right ventricle and the right atrium [difference between peak right ventricular systolic pressure (RVSP) and RA pressure]. Therefore, estimated RVSP is equal to this pressure difference, determined from the peak TR velocity, plus the estimated RA pressure (Table 60.7). If there is no obstruction across the pulmonic valve, the RVSP will be similar to the **PASP**:

$$\text{PASP} = 4 \times (\text{peak TR velocity})^2 + \text{estimated RA pressure}$$

- c. **Pulmonary artery diastolic pressure (PADP).** Pulmonary regurgitation represents the pressure difference between the pulmonary artery (PA) and the right ventricle at end-systole. Hence, the end pulmonary regurgitation velocity can be utilized to measure the end-diastolic pressure difference between the PA and the right ventricle. The right ventricular end-diastolic pressure should be similar to the RA pressure; therefore, addition of estimated RA pressure to the end-diastolic pressure difference between the PA and the right ventricle will estimate the PADP:

$$\text{PADP} = 4 \times (\text{end pulmonary regurgitant velocity})^2 + \text{estimated RA pressure}$$

- d. **Estimated left atrial pressure (LAP) or left ventricular end-diastolic pressure (LVEDP).** Provided that there is no mitral stenosis, LVEDP and LAP should be the same. This important measure of LV diastolic function can be estimated by several methods.
- (1) **Deceleration time (DT) of mitral inflow.** A DT of < 150 milliseconds is strongly suggestive of an elevated LVEDP/LAP. In very young patients, a DT < 150 milliseconds may be normal. This results from a rapid equalization of pressures secondary to vigorous early diastolic relaxation and is not caused by an elevated LAP.
 - (2) **Difference between pulmonary venous atrial duration and mitral atrial duration.** Normally, mitral A wave duration is greater than pulmonary venous atrial reversal (Ar) duration. When LVEDP is increased, the velocity and duration of the mitral A wave decreased, whereas pulmonary vein Ar velocity and duration increased. The difference between the duration of the Ar wave and the mitral A wave correlates with LVEDP. An Ar-A duration of > 50 milliseconds is specific for an elevated LVEDP > 20 mm Hg. This is reliable in patients with reduced EF but not in patients with normal EF. The primary limitation with this method is the difficulty in accurately measuring the duration of Ar.
 - (3) **Combined mitral inflow/CMM index (E/V_p ratio).** This index has been demonstrated to correlate with LAP/LVEDP, especially when these filling pressures are elevated. A ratio of > 2 is suggestive of elevated filling

pressures. In patients with normal EFs, especially with small ventricles and hyperdynamic function, the flow propagation velocities are not accurate.

- (4) **Combined mitral inflow/TDI index** (E/E' ratio). This index has been shown to be a semiquantitative measure of LVEDP. A ratio of > 10 (using the lateral annulus) or > 15 (using the septal annulus) correlates with a wedge pressure of > 20 mm Hg. A ratio of < 8 (using the lateral annulus) correlates well with normal filling pressures. For values that fall in between these two limits, the clinician should look at all the other information provided by echocardiography such as left atrial size and pulmonary venous Doppler to assess whether filling pressures are elevated.
3. **dP/dt** . This index of LV contractility is the rate of pressure increase during isovolumic contraction and is traditionally obtained using invasive pressure transducers. It can be estimated from the CW Doppler of the MR jet. During isovolumic contraction, there is no change in LAP; therefore, MR velocity changes reflect dP/dt , with more rapid increases in MR velocity being associated with increased contractility. The pressure change between 1 m/s and 3 m/s $= 4 (V_2^2 - V_1^2) = 32$ mm Hg. The time it takes the ventricle to accelerate an MR jet velocity from 1 m/s to 3 m/s is measured and then the dP/dt is calculated as follows:

$$dP/dt = 32 \text{ mm Hg/time (in seconds)}$$

This has been demonstrated to correlate well with invasively measured dP/dt . It is considered normal when the calculated value is $> 1,200$ mm Hg/s.

4. **Continuity equation** is an application of the principle of conservation of mass, which states that flow across a conduit of varying diameter is equal at all points. This equation is especially useful in quantifying a stenotic aortic valve area (AVA) that cannot be accurately measured using planimetry from the transthoracic window. Flow at any point in the heart is the product of the cross-sectional area (CSA) and the flow velocity. As flow velocity varies during ejection in a pulsatile system, individual velocities must be integrated to measure total volume of flow (velocity time integral, VTI). This is determined by tracing the spectral Doppler profile, using standard measurement software built into all echocardiography machines.

Flow at any point = CSA \times VTI

Based on the continuity equation, flow through the LVOT must be equal to flow through the aortic valve; therefore, AVA can be calculated following these steps:

Flow across the LVOT = flow across the aortic valve

$$\text{Area}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}} = \text{area}_{\text{aortic valve}} \times \text{VTI}_{\text{aortic valve}}$$

$$\text{Area}_{\text{aortic valve}} = \text{area}_{\text{LVOT}} \times \text{VTI}_{\text{LVOT}} / \text{VTI}_{\text{aortic valve}}$$

$$\text{Area}_{\text{aortic valve}} = (\text{diameter}_{\text{LVOT}}/2)^2 \times \pi \times \text{VTI}_{\text{LVOT}} / \text{VTI}_{\text{aortic valve}}$$

$$\text{Area}_{\text{aortic valve}} = (\text{diameter}_{\text{LVOT}})^2 \times 0.785 \times \text{VTI}_{\text{LVOT}} / \text{VTI}_{\text{aortic valve}}$$

The assumption is that the LVOT cross-section is a circle. The greatest source of error in this equation is in the measurement of the LVOT diameter because the value is squared, resulting in magnification of any initial measurement error. The appropriate place to measure the LVOT can be difficult to define accurately in some calcified valves. The **dimensionless index** (DI) is the ratio of the VTI of LVOT to the VTI of aortic valve, and it is preferable to use this to assess aortic

stenosis when accurate measurement of the LVOT diameter is not possible or in those patients with history of previous aortic valve replacement. A $DI < 0.25$ suggests severe aortic stenosis.

$$DI = VTI_{LVOT} / VTI_{aortic\ valve}$$

Of note, the flow across the LVOT per beat is the SV, which can thus be calculated from the product of the LVOT diameter and flow velocity (VTI_{LVOT})

$$SV = (\text{diameter}_{LVOT})^2 \times 0.785 \times VTI_{LVOT}$$

5. **Volumetric method to assess regurgitant volume/regurgitant fraction.** This is based on the conservation of flow, with total flow across a regurgitant valve being equal to the sum of the forward flow and the regurgitant flow. For example, for MR:

Total transmitral flow volume = forward flow volume (LVOT flow) + regurgitant volume
(LVOT flow can be assumed to be the same as the forward flow provided there is no AR.)

Regurgitant volume = mitral forward flow – LVOT flow

$$\text{Regurgitant volume} = (\text{diameter}_{mitral})^2 \times 0.785 \times VTI_{mitral} - (\text{diameter}_{LVOT})^2 \times 0.785 \times VTI_{LVOT}$$

$$\text{Regurgitant fraction} = \text{regurgitant volume} / \text{total mitral flow}$$

Because of the multiple assumptions and calculations performed, this method is prone to error and is rarely used clinically.

6. **The PISA method** is another application of the principle of conservation of mass. It is based on the phenomenon that flow accelerates proximal to a narrowed orifice. This is illustrated by the acceleration of water in a bathtub before it enters the drain pipe. Using color Doppler, as flow accelerates, its velocity may exceed the Nyquist limit which results in color reversal because of aliasing. This is seen as a series of colored (“isovelocity”) hemispheres with color flow imaging, with the velocity of flow at the surface of this hemisphere being the aliasing velocity (Nyquist limit) of color flow in that direction. Decreasing the aliasing velocity will increase the size of the hemisphere, as the velocity at which color changes is reduced. In keeping with conservation of mass, blood flow at the surface of this hemisphere is the same as flow through the regurgitant orifice, and this is the basis of using the PISA method to estimate the regurgitant orifice area (ROA) of a valve. PISA has been most extensively used to estimate the mitral ROA to quantify MR.

Flow at surface of hemisphere = flow through regurgitant orifice

Surface area of hemisphere \times velocity at hemisphere = $ROA \times$ peak velocity of regurgitation [using continuous wave Doppler (CW) through the mitral valve]

$$2 \times \pi (\text{radius})^2 \times \text{aliasing velocity} = ROA \times \text{peak MR velocity}$$

$$ROA = 2 \times \pi (\text{radius})^2 \times \text{aliasing velocity} / MR_{CW} \text{ peak velocity}$$

Therefore, the radius of the PISA hemisphere, the aliasing velocity, and the peak mitral regurgitation (MR) velocity are the measurements needed for calculating ROA. The greatest source of error is in defining the precise location of the ROA, so as to accurately calculate the radius.

This method can also be used to measure MVA in mitral stenosis (where forward flow convergence is seen and measured) and the aortic ROA in AR, although it may be difficult to obtain satisfactory visualization of the aortic PISA for quantification from the apical long-axis view (best view to appropriately line up AR jet with the Doppler). When the jet is eccentric, and a full hemisphere is not visible, an angle correction should be considered. The PISA equation for MR can be simplified if the aliasing velocity is set to 40 cm/s and it is assumed that peak MR velocity will be 5 m/s (equates to a normal LV-to-LA pressure gradient of 100 mm Hg). Using these two constants, the PISA equation is simplified to

$$\text{ROA} = (\text{radius})^2/2$$

Peak MR velocity will increase or decrease depending on the changes in LV systolic pressure and LAP, and it cannot always be assumed to be 5 m/s. However, this method is useful for semiquantification and rapid assessment. Regurgitant volume can be calculated as follows:

$$\text{Regurgitant volume} = \text{ROA} \times \text{VTI}_{\text{MRjet}}$$

7. Pressure half-time ($P_{1/2}^1$) is used to estimate the MVA, as the time for the pressure to fall by half across a stenotic valve is proportional to the degree of stenosis. It is the time interval for the peak pressure gradient to fall by half. Using the Bernoulli equation to convert pressure to velocity, there is a constant relationship between peak velocity and the velocity at $P_{1/2}^1$.

Pressure at half the peak pressure = 1/2 peak pressure

$$4 \times (V_{1/2}^1)^2 = \frac{1}{2}(4 \times V_{\text{max}}^2) \rightarrow V_{1/2}^1 = V_{\text{max}} \div \sqrt{2}$$

In addition, the $P_{1/2}^1$ has a constant relationship with the deceleration time (DT) of the early mitral filling wave, and it is usually estimated from the following:

$$P_{1/2}^1 = 0.29 \times \text{DT}$$

Hence, $P_{1/2}^1$ can be easily measured by using the DT or by simply measuring the time interval from peak to $\frac{1}{2}$ (which is determined from the V_{max}^1). Most echocardiographic measurement software packages automatically calculate $P_{1/2}^1$ when the slope of the CW Doppler of the mitral inflow jet is measured. For mitral stenosis, an empirical constant has been validated to correlate $P_{1/2}^1$ and MVA:

$$\text{MVA} = 220/P_{1/2}^1$$

This has only been validated for native valves and will overestimate valve areas for prosthetic valves. The other primary use of $P_{1/2}^1$ is to help quantify AR. The $P_{1/2}^1$ of the AR Doppler velocity jet becomes shorter with worsening AR, as the more severe the AR, the more rapidly the pressures in the aorta and the left ventricle equilibrate. A $P_{1/2}^1 < 250$ milliseconds suggests a severe AR. There are many limitations with this, including the fact that $P_{1/2}^1$ is affected by aortic and LV compliance and by a change in systemic vascular resistance.

VII. TECHNICAL ASPECTS AND ADVANCED IMAGE ACQUISITION

A. Machine settings. To obtain the best images and accurate Doppler information, it is important to optimize the machine settings during different parts of the examination (Tables 66.5 and 66.6).

1. **Time gain compensation.** These controls differentially amplify the echo signals returning from different depths to compensate for attenuation of the ultrasound beam with increasing distance from the transducer. This function is useful with

higher frequency transducers, as they are associated with more attenuation at greater depths.

2. **Depth.** Start with the greatest depth to get an overview and then decrease the depth to include all of the target structure. A depth of 16 cm is usually adequate for the apical window and 12 cm for parasternal imaging. Increasing the depth decreases the frame rate, reducing temporal resolution.
3. **Transmit gain.** This adjusts the displayed amplitude (power) of all received signals and, therefore, affects the brightness of echoes displayed. Setting the power too low results in inadequate returning signals and poor image quality, whereas setting it too high results in image whiteout.
4. **Compress.** The compress setting is also known as a **dynamic range**. It converts the range of returning echo intensities, which may vary a billion-fold in intensity, into 100 to 200 visual shades of brightness or the “gray scale.” Increasing the compress will “soften” the image and allow identification of lower level signals. Decreasing the compress results in the production of high-quality contrast images such that weaker signals are eliminated, noise is reduced, and the strongest echo signals are enhanced. Therefore, the compress/dynamic range is decreased when image quality is poor.
5. **Focus (or position).** The focal zone of the transducer indicates the region of the image at which the ultrasound beam is narrowest, and hence where spatial resolution is maximal. Therefore, it is important to reposition the focus to the area of greatest attention/importance, especially those in the near field. When adjusted proximally, however, distal structures may appear blurred as the ultrasound beams scatter.
6. **Persistence.** Persistence is the temporal averaging of the latest frame with the previous frames to produce a smooth or less noisy display. Fast-moving cardiac structures (e.g., valve leaflets) may appear blurred if the persistence is set above low.

B. Imaging artifacts

1. **Acoustic shadowing.** Highly reflective structures block transmission of ultrasound to distal structures, causing poor imaging of these far-field structures. For instance, a mechanical mitral prosthesis prevents good visualization of the left atrium from the apical window.
2. **Reverberation.** This occurs when multiple linear echo signals are generated from a back and forth reflection between two strong reflectors of the ultrasound signal, before the signal returns to the transducer. These appear as multiple parallel irregular dense lines extending from the structure into the far field (e.g., linear echodensity in the ascending aorta in the PLAX view simulating a dissection flap, which is a reverberation from a more anteriorly lying structure, such as a rib). Reverberation artifacts will be present at a multiple of the distance between the two strong reflectors—usually at twice the distance between the strong reflectors. Careful analysis of the artifact in multiple views and with color Doppler should be performed. Color flow signals will be seen to pass through the artifact.
3. **Refraction.** Refraction of the ultrasound beam as it passes through a tissue layer can result in a side-by-side double image. This artifact is often seen in PSAX views of the aortic valve where the image appears to show two aortic valves overlapping.
4. **Beam width artifact.** Ultrasound beams are 3D and are reflected from 3D structures, but they are displayed in a 2D tomographic plane. Strong reflectors at the edge of a central beam, especially outside the narrow proximal focal zone, can be superimposed on a structure in the central zone with the resulting appearance of a structure within the image, that is, outside the 2D tomographic plane (e.g., an aortic valve in the left atrium in the A4C view).
5. **Range ambiguity.** Echo signals from earlier pulse cycles reach the transducer on the next receiving cycle because of re-reflection, resulting in deep structures that

appear closer to the transducer than their actual location, and are manifested as the appearance of an anatomically unexpected echo. This can be confirmed by the disappearance of the artifact when the depth setting is changed.

6. **Side lobe artifacts.** In addition to the central beam, transducers produce side lobes 10° to 30° off axis. All echoes returning from structures in these peripheral beams are displayed, as if they arose from targets within the main beam. Therefore, strong reflectors may be imaged by these low-intensity side lobes and displayed in an erroneous position on the screen. This is a major source of “clutter” in cardiac cavities. Harmonic echoes have much lower intensity side lobes, with a resulting reduction in side lobe artifacts in the image.

- C. **Factors affecting color Doppler image.** Many factors affect spectral Doppler and color flow Doppler, and it is important to consider these. They can be broadly divided into three groups: machine settings, imaging factors, and hemodynamic factors (see Table 67.8 for tips to optimize Doppler settings).

TABLE 67.8 Tips for the Transthoracic Doppler Examination

1. Doppler (all modalities) is very **angle-dependent**—angle between the ultrasound beam and the blood flow jet of interest should be $< 20^\circ$. In order to achieve this off-axis views are often required.

PW and CW Doppler

2. Shifting the **Doppler baseline** up or down can double the maximal velocity detected (still < 2 m/s) for PW.
3. Increasing the **depth** decreases the Nyquist limit and reduces the maximal velocity that can be measured with PW.
4. Recheck high-velocity jets with the **Pedoff (CW)** probe to confirm peak velocity (include right upper sternal border positions when trying to obtain peak aortic stenosis velocity).
5. Start with high-**gain setting** and reduce until noise and clutter are adequately suppressed.
6. Set **wall filter** to low to avoid overestimation of low velocities.
7. Decreasing the **compress** enhances the edges of the spectral envelope, increasing it enhances the various velocities displayed within the Doppler envelope.
8. Initially set “**reject**” at low (20–40%) to allow the display of a wide range of signals, then increase to remove signals that obscure the image (i.e., to reduce noise).
9. Adjust **gate width**—1–2 mm for mitral inflow and LVOT, 3–4 mm for pulmonary venous flow, and 5–10 for Doppler tissue imaging.

Color flow Doppler

10. **Narrow** the sector and minimize the **depth** to maximize color resolution (increase frame rate).
11. Spatial resolution is higher **axial** to the beam than lateral.
12. Higher **transducer frequencies** result in an increased area of flow disturbance (reduces the Nyquist and increases ability to visualize lower velocities)
13. Adjust **color gain** until just before noise appears in the color.
14. Minimize **wall filters** during analysis of PISA/flow convergence, to avoid overestimating low velocities.

(Continued)

TABLE 67.8 Tips for the Transthoracic Doppler Examination (*Continued*)

15. Decreasing the **Nyquist limit** increases the size of any regurgitant jet as lower velocities are detected (normally not color coded at higher Nyquist velocities); therefore, set at 50–60 cm/s initially.
16. Be careful not to miss or underestimate very **eccentric jets** of mitral regurgitation or aortic regurgitation.
17. Remember that **chamber constraint** reduces the size of a jet.

CW, continuous wave; LVOT, left ventricular outflow tract; PISA, proximal isovelocity surface area; PW, pulsed wave.

1. Machine settings

- a. **Nyquist limit.** At any given depth, in color Doppler imaging the Nyquist or aliasing velocity (which is related to the PRF) can be adjusted. Typically, it is set to 50 to 60 cm/s. The lowest velocity that is displayed on the color map is related to the Nyquist (minimal displayed velocity = $\text{Nyquist} \times 2/32$). Therefore, decreasing the Nyquist increases the lowest velocity displayed, which has the effect of increasing the size of the jet area.
- b. **Transducer frequency.** In color flow imaging, higher transducer frequency reduces the peak velocity (Nyquist limit) that can be measured (see Doppler equation above). Lower Nyquist results in an increased color flow jet area. Therefore, higher frequency transesophageal echocardiography generally produces larger areas of flow disturbance than transthoracic echocardiography. In spectral Doppler imaging, lower frequency transducers can measure higher velocities.
- c. **Depth setting.** Minimizing the depth setting to encompass only the region of interest maximizes the PRF and frame rate.
- d. **Gain.** Adjust the color gain until just before random noise appears in the color. Increased color gain increases the size of color flow disturbance. Two-dimensional gain should be decreased during the color Doppler examination to maximize color flow disturbance because each pixel is assigned to either 2D or color. In PW and CW Doppler, start with a high-gain setting until the desired signal is appreciated. The gain is decreased until noise and clutter are adequately suppressed.
- e. **Baseline.** Used primarily for unwrapping aliased signals. Generally leave it in the middle of the color bar, but it can be adjusted to maximize the velocity that can be displayed with PW or color Doppler. This is also useful for highlighting a specific velocity as in proximal convergence analysis.
- f. **Wall filter.** Excludes low-velocity, high-amplitude signals from myocardial motion. If set too high, it tends to decrease the color flow disturbance. A typical initial setting is 400 Hz. The setting of the wall filter should be minimized during analysis of the proximal flow convergence region to avoid overestimation of low velocities (i.e., set low for PW Doppler and high for CW Doppler).
- g. **Beam width.** Beam width is especially important with PW and CW Doppler. As the ultrasound beam propagates, it spreads out. For example, when sampling pulmonary venous flow with pulse Doppler from the apical view, the sample volume may be at 16-cm depth and the ultrasound beam may be > 1 cm in width. This can lead to the detection of aortic flow, which is displayed as if it arose along the beam axis (from the pulmonary vein) leading to beam width artifact.

- h. **Gate length or sample size.** This is the size of the PW Doppler sampling region. It is usually set at 3 to 5 mm. Narrowing the gate focuses the velocity data to a smaller spatial area and can help improve image quality, but it requires very accurate positioning to prevent missing of the appropriate sample area during cardiac motion.
 - i. **Scale.** Controls the range of Doppler velocities displayed. As the velocity scale increases, the velocity limits increase and the displayed waveform size decreases.
 - j. **Compress.** In spectral (PW and CW) Doppler, the compress setting adjusts the gray scale, which controls image softness. Decrease the compress to enhance the edges of the spectral envelope. Increase the compress to enhance the various velocities displayed within the Doppler spectrum. Set at 30 dB or higher initially.
 - k. **Reject.** In spectral Doppler, the reject control removes low-amplitude signals ("noise") from the spectral display. The reject control is initially set at a low level (20% to 40% maximum) to allow the display of a wide range of signals. The reject is then increased to remove signals that obscure the image.
2. **Imaging factors**
- a. **Interrogation angle.** Color flow imaging measures only the component of flow that is parallel to the ultrasound beam. This is related to the true flow velocity by the cosine of the angle between the blood flow and the interrogating ultrasound beam. Satisfactory alignment (as parallel to the flow as possible) is vital to record the full and maximal velocity jet with spectral (both PW and CW) Doppler.
 - b. **Attenuation.** Loss of signal strength caused by too high a transducer frequency for the required depth results in a reduced area of color flow disturbance.
 - c. **Acoustic shadowing.** Loss of signal strength caused by a proximal reflector of ultrasound (e.g., a mechanical prosthetic valve preventing apical imaging of MR jet in the left atrium).
3. **Hemodynamic factors**
- a. **Flow volume.** Increasing regurgitant volume results in an increased area of color flow disturbance, and this is the basis for the common practice of judging the severity of valvular regurgitation by the size of the color jet. However, as outlined in this chapter, many factors affect the size of the color flow jet area. Therefore, it is important to include other factors in the assessment of regurgitation, such as ventricular and atrial sizes, the morphologic appearance of the valve, the width of the color jet at its narrowest point (vena contracta), and, in particular, more quantitative analysis using the proximal flow convergence region (PISA). Several cardiac cycles should be inspected with minor adjustments in the angle of interrogation to ensure that the largest jet is visualized.
 - b. **Driving pressure.** Increased pressure gradient across a regurgitant orifice results in an increased color flow disturbance in the receiving chamber. Color jet size is closely related to jet momentum, given by flow rate multiplied by jet velocity.
 - c. **Chamber constraint in eccentric jets.** Impingement of a regurgitant jet against walls of the receiving chamber will decrease the size of the color disturbance. For example, severe but eccentric MR may have a very small area of color flow disturbance because the jet loses momentum to the constraining left atrial wall and appears narrower in a 2D view as it is splayed out over a larger surface area of the wall.
4. **Doppler artifact.** Mirror image artifact can be seen occasionally when the Doppler signal is duplicated on the other side of the baseline.

ACKNOWLEDGMENTS: *The author thanks Drs. Patrick J. Nash, Steven Lin, Guy Armstrong, and Ron Jacob for their contributions to earlier editions of this chapter.*

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Transesophageal Echocardiography

- I. INDICATIONS.** In general, transesophageal echocardiography (TEE) is performed when there is a clinical question for which the information obtained using transthoracic echocardiography (TTE) is insufficient. This may be to better define pathology that has been identified by TTE or to obtain better images when transthoracic images are inadequate. The close proximity of the esophagus to the heart allows for improved visualization of many cardiac structures, particularly those that are posteriorly located. In addition, higher frequency probes can be used, given the shorter distance between the probe and the heart, further enhancing the resolution. However, imaging planes are somewhat constrained by the relative position of the esophagus and heart, and some structures (e.g., prosthetic aortic valve) and certain Doppler measurements may be better assessed by TTE.

Indications for TEE in various conditions and clinical situations are listed in Table 68.1. Very common indications include examination to rule out a cardiac source of embolus, assessment of valves, prosthesis, and intracardiac device for endocarditis or its accompanying complications, such as abscess. The assessment of native and prosthetic valvular function, in terms of degree and mechanism of regurgitation or stenosis, is a frequent indication for TEE. Acoustic shadowing by prosthetic valves, particularly in the mitral position, poses less of a problem for TEE than it does for TTE. Given the increasing prevalence of atrial fibrillation, another frequent indication for TEE is to assess left atrial and left atrial appendage pathology and function, particularly prior to cardioversion. Congenital cardiovascular abnormalities, intracardiac shunts, as well as intracardiac tumors and masses can also be well delineated by TEE. Because of its ability to assess the ascending aorta, arch, and descending aorta, TEE also has an important role in the diagnosis of aortic dissection, aneurysms, and atheroma. In extremely technically difficult/limited transthoracic study such as in postoperative and mechanically ventilated patients, TEE may be used for usual TTE indications such as the assessment of left ventricular function.

TEE is a useful imaging modality in both the operating room and the cardiac catheterization laboratory. In cardiothoracic surgery, TEE is used to assess the mechanism of valvular abnormalities and subsequently evaluate the efficacy of valve repair or replacement. TEE can be used to guide the location of the aortic cross-clamp so that segments with severe atheromatous involvement can be avoided, thereby reducing the risk of embolization. In addition, TEE can provide an assessment of left ventricular function and regional wall motion. As newer transcatheter approaches have become common, including percutaneous valve procedures, closure of paraprosthetic leaks, atrial septal defects, ventricular septal defects, and patent foramen ovale as well as electrophysiological procedures, TEE has been increasingly utilized to help guide catheter position and placement of percutaneous valve or occluding device and evaluate the success and complications of the procedure.

II. CONTRAINDICATIONS

- A.** There are few **absolute** contraindications to the performance of TEE (Table 68.2). These include the **presence of pharyngeal or esophageal obstruction, active upper gastrointestinal bleeding, recent esophageal or gastric surgery, and suspected or**

TABLE 68.1 **Indications for Transesophageal Echocardiography in Various Conditions and Clinical Situations**

Condition	Indication
Infective endocarditis	<p>Patients with at least moderate pretest probability such as <i>Staphylococcus</i> bacteremia, fungemia, prosthetic valves, or intracardiac device</p> <p>Detection of complications of endocarditis: abscesses and fistula</p>
Cardioembolic source	<p>Identification of left atrial and left atrial appendage thrombus or spontaneous echo contrast</p> <p>Identification of patent foramen ovale, atrial septal defect, or atrial septal aneurysm</p> <p>Identification of aortic atheroma</p> <p>Evaluation of mitral and aortic valve for vegetation, tumors, and valve strand</p>
Valvular heart disease	<p>Evaluation of mechanism and severity of mitral regurgitation</p> <p>Characterization of valvular pathology such as aortic morphology</p>
Prosthetic valves	Evaluation of suspected prosthetic dysfunction (stenosis, thrombosis, or regurgitation)
Atrial fibrillation/flutter	<p>Assessment of left atrial and left atrial appendage thrombus prior to cardioversion (e.g., if atrial fibrillation > 48 h) or ablation</p> <p>Follow-up for resolution of thrombus after anticoagulation prior to cardioversion or ablation</p>
Aortic disease	<p>Evaluation for suspected acute aortic pathology: dissection, aortic trauma, and intramural hematoma</p> <p>Characterization of aortic aneurysm and atheroma</p>
Interventional procedures	Guiding performance of interventional cardiac procedures (e.g., percutaneous valve procedure, balloon valvuloplasty, closure of paraprosthetic leak, ASD, VSD, or PFO)
Intraoperative	Assessment of valve repair/replacement and evaluation of systolic function
Intracardiac masses	Detection of characterized masses such as tumors and thrombus
Critical care	<p>Assessment of suspected papillary muscle rupture</p> <p>Assessment of mechanical complications of acute myocardial infarction or mural thrombus</p> <p>Evaluation of unexplained hypotension, especially in the ICU</p> <p>Assessment of early postoperative bleeding, which may result in localized accumulation of blood clots (especially posteriorly)</p>
Congenital heart disease	<p>Identification of site of origin and initial course of coronary arteries</p> <p>Detection of intracardiac shunts</p>

ASD, atrial septal defect; VSD, ventricular septal defect; PFO, patent foramen ovale; ICU, intensive care unit.

TABLE 68.2 Transesophageal Echocardiography Contraindications**Absolute**

Esophageal or pharyngeal obstruction
 Suspected or known perforated viscus
 Gastrointestinal bleeding that has not been evaluated
 Instability of cervical vertebrae

Relative

Esophageal varices or diverticula
 Cervical arthritis
 Oropharyngeal distortion
 Bleeding diathesis or overanticoagulation
 Uncooperative patient

known perforated viscus. If there is instability of the cervical vertebrae, then the examination cannot be performed.

- B. **Relative** contraindications include the **presence of esophageal varices** and **suspected esophageal diverticulum**. In these cases, it is prudent to obtain gastrointestinal evaluation before proceeding, if the study must be performed. Severe cervical arthritis, in which patients may have difficulty with neck flexion, may make it difficult to pass the probe. Oropharyngeal pathology, anatomic distortion, or extreme muscle weakness can likewise make it difficult to proceed with the examination.
- C. **Severe cardiopulmonary disease** is not a contraindication to evaluation by TEE (on the contrary, TEE can often provide critical information when used in these patients), but the operator must be particularly careful to minimize any stress on the patient. This is particularly true in **suspected aortic dissection**, where any sudden increase in blood pressure caused by patient discomfort could result in extension of the dissection. In cases where there is **respiratory instability**, endotracheal intubation with assisted ventilation should be considered prior to the procedure. Patients who are **hypotensive** may not be able to receive sedative agents, as these agents could lead to further hemodynamic compromise. In such patients, the examination may have to be performed with topical anesthesia alone. This is obviously much more difficult for the patient, and TEE should be done only if critical information is not obtainable by other methods.
- D. Given the invasive nature of the procedure, prudence must be observed in patients who are prone to **bleeding**. The procedure is commonly performed on patients who are anticoagulated, such as in those with atrial arrhythmias prior to cardioversion. However, there is increased risk in those who are overanticoagulated. Although no set guidelines exist, it would seem advisable to **delay the examination if possible in patients with an international normalized ratio > 5 or a partial thromboplastin time > 100 seconds**. **Thrombocytopenia** may also increase the risk, particularly with platelet counts $< 50,000/\text{mm}^3$. TEE can still be performed if needed, as the absolute risk remains low, but meticulous attention must be given to nontraumatic esophageal intubation.
- E. **Esophageal infections**, such as those that occur in the context of human immunodeficiency virus (HIV), do not necessarily represent contraindications to the procedure. **Patient discomfort** caused by the presence of the probe in the esophagus may preclude the examination. Universal precautions should be followed (as they should for any patient). The standard disinfectants used to clean the probe will inactivate HIV.

- F. A patient who is very uncooperative is at significant risk for complications from the procedure. In such a case, consideration should be given to aborting the TEE or to increase the level of sedation and prophylactic endotracheal intubation if required.

III. PERSONNEL. The American Society of Echocardiography has proposed the following guidelines for operators who wish to perform TEE: as background, attainment of at least level 2 experience in transthoracic echocardiogram; a minimum of 25 esophageal intubations under guidance; and a minimum of 50 supervised TEE examinations during training. Furthermore, operators should perform a minimum of 25 to 50 TEE examinations yearly to maintain competency.

The presence of a skilled assistant is invaluable during the procedure. The assistant should be either a sonographer or a registered nurse. The role of the assistant is to monitor vital signs during the procedure, ensure proper suctioning of oropharyngeal secretions, and administer medications.

IV. EQUIPMENT. Necessary equipment is listed in Table 68.3.

V. THE TRANSESOPHAGEAL PROBE. The probe is a modification of the standard gastroscope, with transducers in place of fiber optics. The conventional rotary controls with inner and outer dials are present. The inner dial typically guides antelexion and retroflexion, whereas the outer dial controls medial and lateral movement of the tip. A locking mechanism is present, which must not be in effect when the probe is advanced or withdrawn, as esophageal trauma may result. The multiplane probe also has a lever control to guide rotation. Biplane probes are no longer in common use, as they require switching between the transverse and longitudinal planes by a control switch on the echo machine. Advancement and withdrawal of the probe, rotation of the probe about its long axis, and the manipulations available using the above rotary controls constitute the means by which specific images can be obtained (Fig. 68.1).

TABLE 68.3 **Equipment for Transesophageal Echocardiograph**

1. Echo machine and probe (calibrate prior to intubation)
2. Sphygmomanometer
3. ECG rhythm monitor
4. Pulse oximeter
5. Supplemental oxygen
6. Wall suction with Yankauer
7. Intravenous lines and tubing
8. Topical anesthetic agents
9. Sedative medications
10. Bite block
11. Gloves and goggles
12. Emergency equipment
 - a. Drugs (e.g., atropine, epinephrine, naloxone, flumazenil, and lidocaine)
 - b. Defibrillator
 - c. Intubation supplies

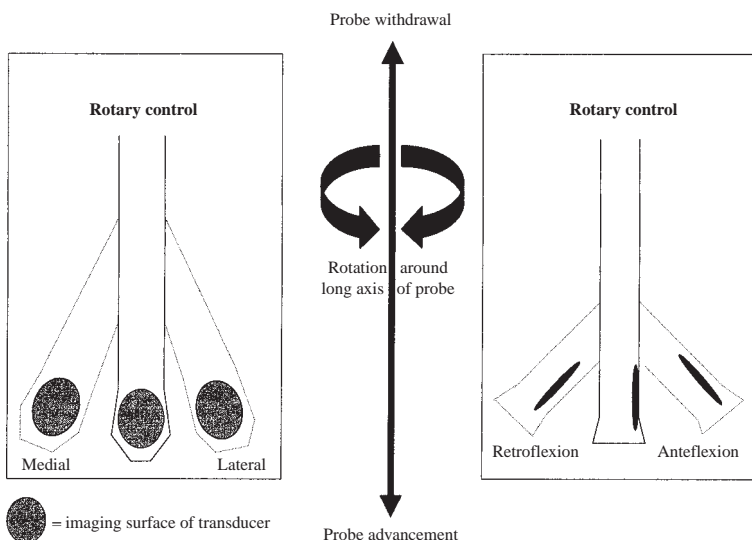


FIGURE 68.1 Specific images can be obtained by advancement and withdrawal of the probe, by rotation of the probe about its long axis, and by the manipulations that are possible using rotary controls.

VI. PATIENT PREPARATION (Table 68.4). The patient should have had nothing by mouth (NPO) for at least 4 to 6 hours before the procedure. Water is allowed up to 2 hours before the test. The clinician can rule out possible contraindications by asking for a history of odynophagia or dysphagia. It is important to be aware of any history of radiation therapy to the mediastinum or cervical region that may have resulted in stricture formation.

The extent of previous workup for any history of gastrointestinal bleeding must be reviewed. The clinician should review recent laboratory studies, paying particular attention to platelet count, hemoglobin level, and coagulation profile. Appropriate inquiries should be made with regard to allergies and former tolerance of sedative medications. The clinician should ensure that the patient understands the procedure, including risks and benefits, and that proper informed consent is obtained and documented before proceeding.

TABLE 68.4 Preparation for Transesophageal Echocardiography

Patient must have had nothing by mouth (NPO) for at least 4 h prior to the procedure

Assess for possible contraindications:

History of odynophagia or dysphagia

History of mediastinal or cervical radiation that might have resulted in stricture formation

History of and workup for gastrointestinal bleeding

Allergies to and previous tolerance of sedative medications

Patient understanding of procedure and indications

Informed consent of patient

VII. STEP-BY-STEP GUIDE TO THE EXAMINATION

- A. The patient's **dentures** should be removed.
- B. An **intravenous (IV) line** should be inserted to allow for administration of medications and saline contrast for study.
- C. The American Heart Association does not recommend **antibiotic prophylaxis** for patients undergoing endoscopic procedures. The reported incidence of transient bacteremia with endoscopy is no higher than the contamination rates reported with blood cultures.
- D. A **blood pressure cuff** should be placed on the patient's arm.
- E. **Electrocardiographic leads** should be applied and connected to the telemetry monitor.
- F. A **pulse oximeter** should be applied to the patient's finger or ear.
- G. A **nasal cannula** should be used so that supplemental oxygen can be given as needed.
- H. While sitting up, the patient should be asked to gargle **viscous 2% lidocaine** for 1 minute and then swallow it for topical anesthesia. **Lidocaine (xylocaine) spray (4%) or Cetacaine spray (10%)** is then sprayed on to the posterior tongue and upper pharynx. These procedures normally suppress the **gag reflex**, but if necessary, this can be verified using a tongue depressor or gloved finger; additional **topical anesthesia** is then applied until the reflex is dulled. By visualizing the area being sprayed, inadvertent spraying of the vocal cord and resultant laryngospasm can be avoided. Methemoglobinemia has been reported with the use of benzocaine-containing product (e.g., Cetacaine), which is usually manifested as central cyanosis and desaturation and can be treated with supplemental oxygen and methylene blue. Some operators advocate the use of drying agents to minimize oropharyngeal secretions (e.g., glycopyrrolate). We generally have not found a need for use of such agents, which can cause an increase in heart rate.
- I. Have the patient lie down on the left side (left lateral decubitus position), facing the echo machine (alternatively, the patient can lie on the right side, with the machine on the right), with neck flexed. TEE can be performed with the patient sitting, but is easier in the lateral position.
- J. **Midazolam**, a benzodiazepine, is the preferred agent for sedation, having the benefit of a short half-life. It also produces an antegrade amnesic effect and has anxiolytic properties. Typically, administer IV doses of 0.5 to 1 mg every 3 to 5 minutes until adequate sedation is achieved. The goal is to reduce anxiety without compromising respiratory drive and while maintaining the patient's ability to follow simple commands, such as swallowing when necessary. Check pulse oximetry and blood pressure before each dose. **Fentanyl**, a short-acting opioid analgesic, can be used for sedation (typically 25 µg IV per dose) in conjunction with midazolam and may be better tolerated in patients with poor left ventricular function or renal impairment. An alternative sedative is **meperidine**, which is typically given in 12.5 to 25 mg IV doses. Meperidine possesses an analgesic effect and helps to suppress the gag reflex as well. Again, **check vital signs before and after each dose**. Additional doses of these sedatives and anxiolytics may be administered during the procedure if necessary. Sedation can lead to potential respiratory suppression; therefore, a benzodiazepine antagonist (e.g., flumazenil 0.2 to 0.6 mg IV) and an opiate antagonist (e.g., naloxone, increments of 0.1 to 0.2 mg IV doses) should be available if required.
- K. With adequate sedation and topical anesthesia (diminution of gag reflex), **begin probe insertion**. There are two approaches that are generally used.
 1. The first is the **digital technique**, which is especially useful with the larger multiplane probe. With this method, the bite guard is inserted onto the shaft of the probe such that after esophageal intubation the bite guard can be moved into place. The distal end of the probe is lubricated. The imaging surface of the transducer is placed toward the tongue. The tip of the transducer is placed under the index finger, and it is slowly guided downward and posterior to the hypopharynx. At this point the patient is asked to swallow, and gentle pressure is applied with the other hand to guide the probe down. Swallowing results in relaxation of the upper

esophageal sphincter. If resistance is met, stop, let the patient relax, and reattempt or redirect as needed. Using the finger as a guide will help center the probe in the region of the hypopharynx over the esophagus and avoid the lateral recesses.

2. An **alternative method is to use the rotary controls on the TEE probe** to guide the intubation. The bite guard is inserted first. The probe is inserted through the bite guard, and gentle antelexion is applied as the probe is passed over the back of the tongue. The probe is then returned to the neutral position, or with slight retroflexion, as it is passed down into the esophagus. The patient is asked to swallow as the probe is advanced past the upper esophageal sphincter. The operator is still able to guide the probe if needed by insertion of a finger around the side of the bite guard.

Patients often gag as the probe enters the upper esophagus (even with adequate anesthesia); however, patients generally find it more comfortable once the probe has passed beyond this point (usually at 25 cm, past the level of the carina). The probe should be advanced to approximately 30 to 40 cm (midesophageal level).

In intubated patients, it is important to **secure the endotracheal tube firmly to one side of the mouth** to prevent dislodgment and inadvertent extubation. Direct visualization with a laryngoscope may be needed. **Sedation** is equally important in these patients, and given the tendency for partially sedated patients to bite on their tubes, a **paralyzing agent** is often required. Intubation in the supine position is not a problem because the airway is protected. Other catheters in the esophagus, such as feeding tubes or nasogastric tubes, often have to be removed prior to the procedure; they may become interposed between the esophagus and the TEE probe, interfering with the images. If left in, these tubes may become dislodged by the TEE probe, and tube position should be reconfirmed after the echocardiographic examination.

For patients with tracheostomies, some operators will carefully and gently deflate the cuff to facilitate probe insertion.

VIII. IMAGING. TEE technology has undergone much evolution, from the initial monoplane views to the current multiplane views. Monoplane TEE provides for images in the horizontal plane only, perpendicular to the shaft of the endoscope. Longitudinal relationships among cardiac structures are difficult to appreciate. With biplane TEE, the orthogonal longitudinal plane can also be obtained. Both monoplane and biplane systems required additional manipulation to obtain off-axis views, making the examination more difficult and more uncomfortable for the patient. With **multiplane TEE**, the transducer has a single array of crystals that can be rotated 180° around the long axis, producing a continuum of transverse and longitudinal images from a single probe position. This minimizes the probe manipulation necessary to obtain intermediate and off-axis images. Consequently, multiplane TEE has increased sensitivity for the detection of sometimes subtle abnormalities, including vegetations, periprosthetic leaks, left atrial appendage thrombi, and aortic dissection. The development of **real-time three-dimensional (3D) TEE** (see Section **VIII.C**) offers the possibility of assessing cardiac structures volumetrically. It has emerged as a clinically relevant modality by providing relatively high image quality, which may enhance clinical decision making especially in regard to structures with a complex anatomy such as the mitral valve. However, this technology is still evolving, particularly with regard to its value in routine clinical practice.

- A. **Basic views.** The TEE examination tends to be more goal directed than the trans-thoracic examination, as there may be time constraints imposed by how long the patient can tolerate the esophageal probe. Initial views should focus on the question at hand, but it is still important to perform a comprehensive and thorough examination. Most operators prefer to begin with upper esophageal views before proceeding to transgastric views. The order of views obtained is not important, provided the operator develops a consistent and comprehensive approach.

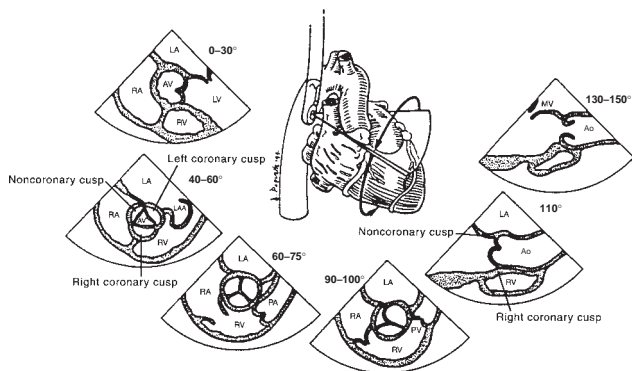


FIGURE 68.2 Schematic representation of selected multiplane transesophageal echocardiography views of the aorta and aortic valve from the upper esophagus. Ao, aorta; AV, atrioventricular; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle; PA, pulmonary artery; PV, pulmonary valve; LAA, left atrial appendage; MV, mitral valve. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

The probe may inadvertently rotate during insertion and may require initial manipulation before starting the examination. The left atrium should be seen at the center of the screen. If the aorta is seen (which is posterior to the esophagus), then the probe must be rotated anteriorly. Slight retroflexion of the probe may be necessary to maintain adequate contact between the probe and the esophagus. Air in the esophagus, which is interposed between the probe and the heart, may affect image quality. This generally lessens as the examination progresses (from ongoing peristaltic activity in the esophagus). Similarly, the presence of a hiatal hernia may compromise image quality.

Views obtained from multiplane TEE are described first. These views are described in terms of degrees of rotation required to obtain particular images. At each transducer location, start array at 0° and rotate to 180° at 5° to 15° increments to obtain a complete sweep. The standard horizontal plane is designated as 0°. At approximately 45°, short-axis views are obtained. Ninety degrees is defined as the longitudinal plane, whereas at around 135°, the true long-axis cardiac views are obtained. At 180°, a mirror image view of the standard horizontal plane is obtained. Given the variable anatomic relationships between structures, the degree of probe manipulation required to obtain the standard views will vary from patient to patient.

1. **Upper esophagus (30 cm)—base of the heart** (Fig. 68.2). With the array at 0°, a five-chamber cross-sectional view of the left atrium, left ventricle, right atrium, right ventricle, and aortic valve is obtained. At 40° to 60°, the three leaflets of the aortic valve become visible (right coronary cusp at the bottom of the screen, noncoronary cusp on the top and to the left, and left coronary cusp on the right). Planimetry of the aortic valve orifice is often possible in this view. Subtle in-and-out movements allow for visualization of the proximal coronaries. The left atrial appendage is also seen in this view (zooming in on the atrial appendage, with subsequent rotation of the array, facilitates inspection for thrombus). At 60° to 100°, the tricuspid valve and right ventricular outflow tract/pulmonary valve become visible. At 120°, long-axis images of the left ventricular outflow tract, aortic valve (noncoronary and right coronary cusps), and proximal ascending aorta are seen. Slight withdrawal of the probe at 110° to 120° permits visualization of the ascending aorta. With the probe withdrawn further into the upper esophagus (Fig. 68.3), the pulmonary artery and its bifurcation can be visualized (from 0° to 45°).

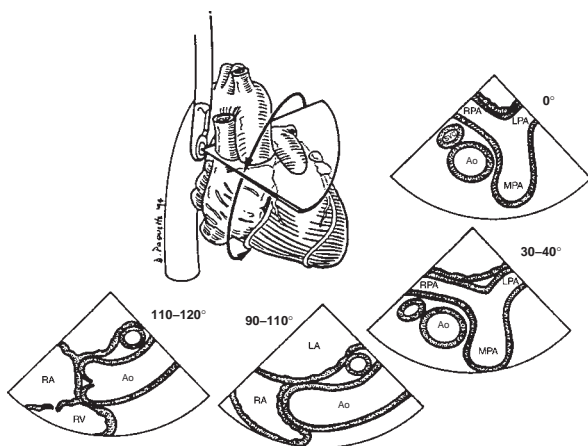


FIGURE 68.3 Schematic of some of the multiplane transesophageal echocardiography views of the aorta and pulmonary artery that can be obtained from the upper esophagus. Ao, aorta; LA, left atrium; LPA, left pulmonary artery; MPA, main pulmonary artery; RA, right atrium; RPA, right pulmonary artery; RV, right ventricle; SVC, superior vena cava. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

2. **Lower and middle esophagus** (Fig. 68.4A and B). With the array at 0°, a four-chamber view is obtained (some retroflexion of the probe is needed for a true four-chamber view, as with antelexion one will see portions of the left ventricular outflow tract and aortic valve). This view is similar to an inverted transthoracic apical four-chamber view. With the left atrium and left ventricle kept in the center of the view field, rotation of the array allows for a thorough evaluation of the left-sided structures. Doppler interrogation of mitral inflow is generally performed with the array at 0° to 30°. Skillful maneuvers as the array is rotated to 90° allow for interrogation of both leaflets of the mitral valve, including the specific scallops of the leaflet. Rotation of the array to 90° to 110° reveals the two-chamber view (left atrium/left ventricle), with the anterior and inferior walls of the left ventricle visualized. The left atrial appendage and the left upper pulmonary vein are also seen. Long-axis views of the left ventricular outflow tract, aortic valve (right and noncoronary cusps), and proximal ascending aorta are obtained by rotation to 120° to 140°. The anterior mitral leaflet is particularly well visualized in these views. This complete sweep permits full delineation of the extent of mitral regurgitation.

Similar views of right-sided structures and the interatrial septum can also be obtained from this position. At 0° (in the four-chamber view as described previously), the septal and anterior leaflets of the tricuspid valve can be seen. The endoscope is then rotated to bring the interatrial septum and the right atrium to the center of view (some withdrawal or advancement of the probe may be necessary to optimize visualization of the interatrial septum). By rotation of the multiplane array, the interatrial septum and fossa ovalis can be thoroughly examined for evidence of a patent foramen ovale or atrial septal defect. Agitated saline contrast can be given intravenously at this time to expose evidence of shunting; asking the patient to perform Valsalva maneuver or to cough can help identify right-to-left shunting. At approximately 100°, the superior vena cava and inferior vena cava can be seen entering the right atrium, and the right atrial appendage

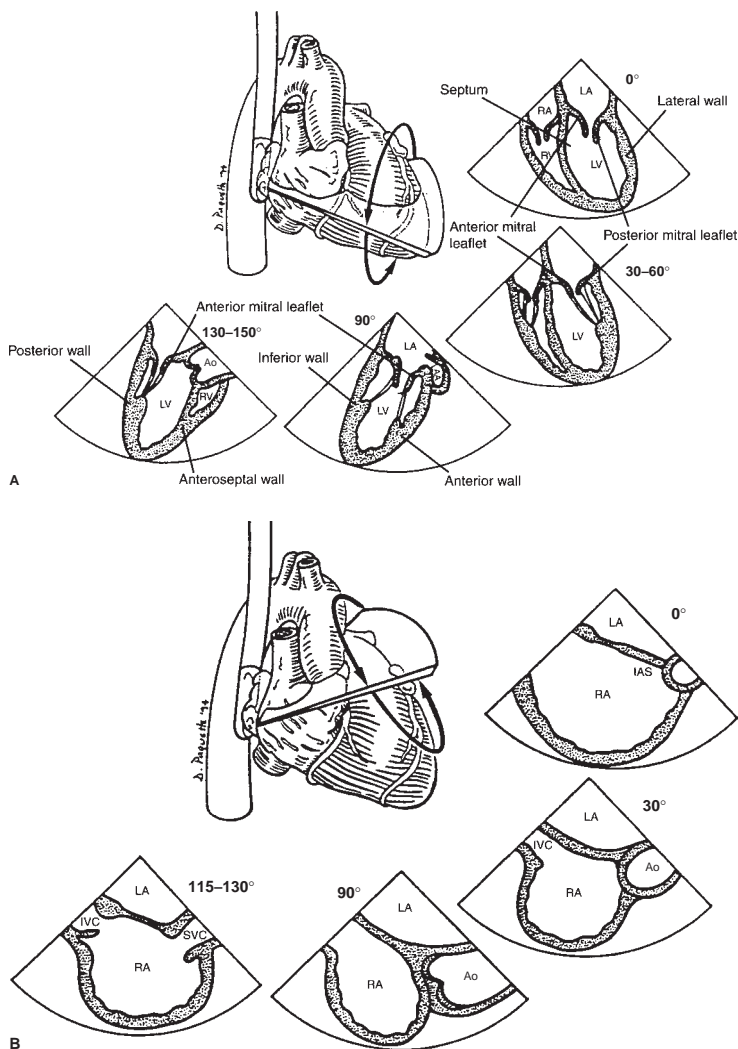


FIGURE 68.4 **A:** Schematic diagram showing some representative sections of the left heart that can be obtained with multiplane transesophageal echocardiography from the lower and middle esophagus. AA, left atrial appendage; Ao, aorta; LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68. **B:** Schematic diagram showing representative multiplane transesophageal echocardiography sections of the atria and interatrial septum that can be obtained from the lower middle esophagus. Ao, aorta; IVC, inferior vena cava; LA, left atrium; RA, right atrium; SVC, superior vena cava; IAS, interatrial septum. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

can also be seen. This is a good view to identify anomalous pulmonary venous drainage into the right atrium or superior vena cava or a sinus venosus atrial septal defect. Further rotation will allow for assessment of the right pulmonary veins.

3. Transgastric views

a. **Proximal** (Fig. 68.5A). These are images obtained from the fundus of the stomach. A cross-sectional view of the left and right ventricles is obtained

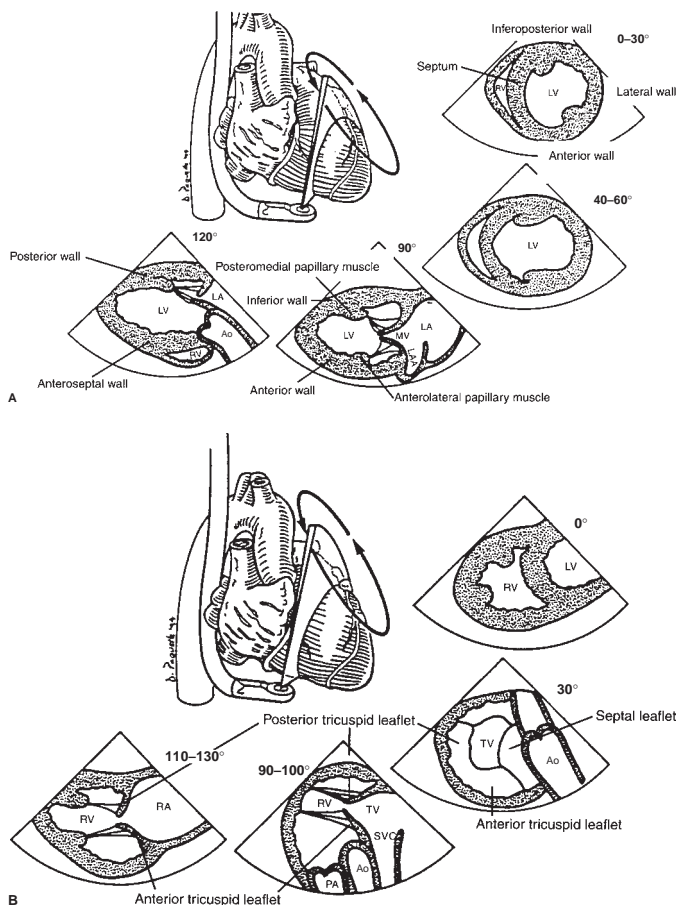


FIGURE 68.5 **A:** Schematic diagram showing representative multiplane transesophageal echocardiography sections of the left heart from the proximal transgastric location. Ao, aorta; LA, left atrium; LV, left ventricle; RV, right ventricle; SVC, superior vena cava; LAA, left atrial appendage; MV, mitral valve. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68. **B:** Schematic of images from a transgastric, multiplane sweep through the right ventricle. LV, left ventricle; RA, right atrium; RV, right ventricle; TV, tricuspid valve; SVC, superior vena cava; PA, pulmonary artery; Ao, aorta. Modified from Roelandt JRTC, Pandian NG, eds. *Multiplane Transesophageal Echocardiography*. New York, NY: Churchill Livingstone; 1996:15–68.

at 0°. By rotating the shaft of the endoscope to center with the left ventricle in the field of view, serial short-axis (“doughnut”) views of the left ventricle can be obtained. Anteflexion of the probe will give rise to basal views, with the mitral and tricuspid valves seen in cross section. With the transducer in a more neutral position, middle and apical short-axis views will be obtained.

At 80° to 100°, a two-chamber view of the left atrium (with appendage) and left ventricle (anterior and inferior walls of the left ventricle, mitral leaflets, and papillary muscles) will be obtained. At $\geq 120^\circ$, a long-axis outflow tract view with aortic valve and ascending aorta will be visualized. The antero-septal and posterior walls of the left ventricle are seen. Depending on the alignment with the transducer, this view may be useful in obtaining velocities across the aortic valve.

Bringing the array back to 0° and rotating the shaft of the endoscope to center the right ventricle in view will allow for interrogation of the right-sided structures (Fig. 68.5B). At 30° to 60°, the three leaflets of the tricuspid valve are visualized (anterior leaflet at the bottom, posterior leaflet on the top, and septal leaflet to the right). At around 70° to 80°, the right ventricular inflow tract view (superior vena cava and tricuspid valve with anterior and posterior leaflets) is obtained. At 90° to 100°, the right ventricular outflow tract and pulmonary valve become visible as well. At 110° to 130°, the two-chamber view of the right ventricle and right atrium can be seen. By rotating to 130° to 150°, the papillary muscles and chordae supporting the tricuspid valve are further delineated.

- b. Deep transgastric.** The probe is advanced further into the stomach with the tip anteflexed. At 0°, a foreshortened five-chamber view is obtained. This view allows for Doppler interrogation of the aortic valve and left ventricular outflow tract. By rotating the multiplane array, different segments of the left ventricle apex can be visualized in the search for thrombus or aneurysm.
- 4. Aorta.** Counterclockwise rotation of the endoscope brings the aorta into view. Typically, the probe is advanced beyond the diaphragm and then slowly pulled back, following the aorta back to the arch. Rotation of the probe is required to keep the aorta in view in the center of the screen. At the level of the diaphragm, the aorta is posterior to the esophagus. In the midesophagus, the aorta is medial, whereas the ascending aorta and arch lie anterior to the esophagus. At 0°, the aorta is seen as a circular structure. Long-axis images (at 100° to 130°) provide additional information as needed at selected intervals. At the arch, the aorta is curved in front of the esophagus, presenting a sausage-shaped structure with the probe at 0°. Gentle clockwise rotation will follow the arch back to the ascending aorta. The ascending aorta is visualized in the longitudinal planes as discussed with the other views. Multiplane TEE has reduced the so-called blind spot of the ascending aorta (where the trachea is interposed between the esophagus and aorta, an area that poses a problem during horizontal plane imaging).
- B. Biplane probe.** There are times during which a biplane probe may be used. This is a smaller probe, so it may be beneficial to use in certain cases when there might be difficulty in esophageal intubation with the multiplane probe. By manipulating the probe via rotation about the long axis and using rotary controls, intermediate and off-axis images in addition to the standard transverse and longitudinal views described earlier can be obtained. Through hands-on experience, the operator will come to be familiar with these maneuvers.
- C. Three-dimensional probe.** The current 3D TEE probes use fully sampled matrix array transducers, allowing a pyramidal volume of data to be acquired. Besides standard two-dimensional imaging modalities, this transducer is able to perform

3D imaging in several modes: live X-plane imaging, live 3D echo, live 3D zoom, triggered full volume, and triggered 3D color. Real-time X-plane imaging allows simultaneous biplane imaging from the same heart beat. Live 3D mode displays real-time 3D images with a small pyramidal segment; 3D zoom mode displays the region of interest with a larger pyramidal segment in real time. Full volume mode acquires wider segment over several cardiac cycles, and color Doppler can also be added in this mode. Three-dimensional TEE is useful for the evaluation of native valves (in particular mitral valve and aortic valve), prosthetic valves, interatrial septum, and left atrial appendage and for the guidance of percutaneous interventional procedures (in particular mitral valve repair, aortic valve implantation, closure of atrial septal defect, and paraprosthetic leaks).

IX. PATIENT RECOVERY. The patient's NPO status should be maintained until the gag reflex has returned. The patient should be instructed to avoid oral intake for at least 1 to 2 hours after the test. When the patient commences oral intake, he or she should initially take a small sip of cold water. If the water does not feel cold in the back of the throat, then some topical anesthetic effect is still present. The patient should wait for another half hour and test the throat again. Until this has dissipated, the patient should avoid any hot drinks so as to avoid scalding. Appropriate precautions should be followed if sedatives were used, as the effects persist for several hours. Patients may have dizziness and orthostatic symptoms for up to several hours and should be instructed to sit or lie down if this occurs. Patients should not drive or operate heavy equipment until the next day.

X. PROBE CARE. Following use, the probe should be cleaned with soap, water, and an enzymatic solution to remove saliva. The nonimmersible parts of the probe, such as the handle and rotary controls, should be cleaned with alcohol. Afterward, the probe should be soaked in a glutaraldehyde solution for a minimum of 20 minutes and a maximum of several hours to eliminate bacteria. The probe should not be soaked in this solution overnight. It can then be rinsed with water and air-dried. The probe should be inspected closely for any tears or perforations.

XI. COMPLICATIONS. In reported series, the incidence of major and minor complications is 2% to 3%, with most being minor complications. Major complications (death, esophageal perforation, significant arrhythmias, congestive heart failure, and aspiration) occur with a frequency of 0.3%, with a reported mortality of < 0.01%. Reported minor complications include transient hypotension, hypertension (particularly with agitation), transient hypoxia, transient bronchospasm, and arrhythmias (such as supraventricular tachycardia, nonsustained ventricular tachycardia, and transient atrioventricular block). Methemoglobinemia has been rarely reported due to the anesthetic spray and should be considered if cyanosis occurs. Other complications of intubation include tracheal intubation, laryngospasm, and vocal cord paralysis. Sore throat is not uncommon after the procedure and may persist for a day. Anaphylaxis and other allergic reactions can occur due to the medications used.

XII. PITFALLS. The improved resolution and anatomic detail provided by TEE, as compared with TTE, is what makes it such a powerful diagnostic tool. However, this can also lead to misinterpretation of normal structures. Trabeculations in the atrial appendage can be mistaken for thrombi, and lipomatous hypertrophy of the interatrial septum can be incorrectly labeled as a mass, as can the eustachian valve. The transverse and oblique sinuses can be mistaken for abscess cavities. Off-axis images may create the appearance of a mass on the aortic valve when one of the cusps is cut obliquely. The lungs can give rise to reverberation artifacts, which can erroneously be diagnosed as dissection flaps (presence in nonanatomic planes, lack of disruption of color Doppler of blood flow, and crossing of

normal anatomy all favor diagnosis of artifact). Abnormal findings should be visualized and verified in several views to ensure that they do not represent imaging artifacts.

These pitfalls are best minimized by the experience of the operator, but variations in anatomy may provide diagnostic dilemmas for even the most skilled echocardiographer.

ACKNOWLEDGMENTS: *The authors wish to thank Deepu Nair, MD, for his contributions to a previous edition of this chapter.*

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Pericardiocentesis

I. INTRODUCTION. Pericardiocentesis is an important therapeutic and diagnostic procedure in cardiology. Most often, it is used to relieve tamponade and identify causes of pericardial effusions. When performed correctly by experienced operators, pericardiocentesis has proven to be both an effective and safe procedure.

II. INDICATIONS

A. Alleviation of cardiac tamponade. Cardiac tamponade is a clinical diagnosis classically characterized by hypotension, tachycardia, distended neck veins, pulsus paradoxus, and distant heart sounds. Echocardiographic data provide confirmatory evidence for this diagnosis and include effusion (regional or circumferential), inferior vena cava plethora, diastolic collapse of the right atrium and right ventricle, and increased respiratory variation of blood flow through the tricuspid and mitral valves. The normal pericardial cavity typically contains 15 to 50 mL of fluid. **The additional volume of fluid required to cause hemodynamic compromise is variable** and is dependent upon several factors, including the patient's volume status, the rapidity of fluid accumulation, and intrathoracic pressure (positive end-expiratory pressure increases intrathoracic pressure, impairing right heart filling and exacerbating tamponade physiology). Therefore, a relatively small but rapidly accumulating effusion can cause tamponade, particularly in the intravascularly depleted patient.

B. Evaluation of and therapy for pericardial effusion

- 1. After open heart surgery.** Effusions after open heart surgery are common; rarely, they may be of hemodynamic significance. Data from the Mayo Clinic suggest that the incidence of significant effusion in patients 18 years of age or older up to 30 days after cardiac surgery with cardiopulmonary bypass is 1.5%. The risk of effusion is highest in patients undergoing heart transplant and lowest in patients undergoing coronary artery bypass grafting. Renal failure, immunosuppression, pulmonary thromboembolism, prolonged cardiopulmonary bypass, and high body surface area were all independent risk factors for significant effusion. The contribution of anticoagulation to effusion formation is less established, but it is likely a risk factor as well. It should be noted that approximately **50% of patients who were discharged with a small clinically insignificant pericardial effusion, especially those status post valve surgery, required readmission** approximately 2 weeks after surgery for treatment of tamponade.
- 2. Idiopathic.** In patients presenting with large, idiopathic effusions, evaluation of pericardial fluid—including cytologic examination, culture, cell counts, and chemistries—frequently assists in diagnosis. In fact, data suggest that the causes of most effusions can be diagnosed with history, physical examination, laboratory evaluation, and pericardial fluid analysis. Fluid analysis has been shown to be more helpful than pericardial tissue biopsy for culture of viral and bacterial

pathogens, and cytology is positive in 65% to 85% of cases of malignant effusion. Some experts recommend that large pericardial effusions (> 20 mm) be drained if the effusion persists for more than 1 to 3 months. **Up to one-third of patients with large idiopathic pericardial effusions develop cardiac tamponade unexpectedly.**

3. **Malignant.** Malignant pericardial effusions are a rare manifestation of metastatic disease. Fluid cytology is usually positive and can be of value if the primary tumor is unknown. Lung, breast, and hematologic cancers are the most common etiologic factors. Controversy exists regarding the most appropriate management of malignant effusions. There are no prospective, definitive studies comparing surgical management and pericardiocentesis. Frequently, surgical approaches are used because of concerns about reaccumulation. Large malignant effusions treated with simple pericardiocentesis without prolonged catheter drainage reaccumulate in as many as 60% of cases. However, several studies have indicated that when a pericardial drain is left in place for several days until drainage is < 25 mL/d (average 4.8 days), the risk of reaccumulation is low—approximately 12%. Sclerotherapy has a similar failure rate, and the 30-day mortality risk of a pericardial window is approximately 8%. Therefore, pericardiocentesis with drain placement is a very reasonable initial procedure for the diagnosis and management of malignant effusions.

III. CONTRAINDICATIONS

A. Absolute. In emergent scenarios of cardiac tamponade, when circulatory collapse is imminent, there are no absolute contraindications. In these instances, pericardiocentesis is often a lifesaving intervention.

B. Relative

1. **Anticoagulation.** The risk of bleeding is low with pericardiocentesis; however, if time permits, prothrombin time and partial thromboplastin time (PTT) should be obtained in all patients undergoing pericardiocentesis. An international normalized ratio > 1.8 or PTT greater than twice the normal should be allowed to normalize or be managed with fresh frozen plasma before intervention. It should also be noted that **tamponade physiology, by leading to hepatic congestion, may produce or exacerbate coagulation abnormalities.**
2. **Thrombocytopenia.** Platelet counts should be > 50,000.
3. **Traumatic hemopericardium.** A patient with traumatic hemopericardium should be treated surgically.
4. **Type A aortic dissection.** Typically, hemorrhagic effusions secondary to type A dissections are treated emergently with surgery. However, in situations where tamponade and circulatory collapse are imminent, small volume (10 to 25 mL) pericardiocentesis is indicated to stabilize patients before surgery. Data suggest that larger volume taps may be detrimental. In general, however, effusions in the setting of a type A dissection should be treated with emergent surgery.
5. **Subacute free wall rupture.** As with dissections, free wall ruptures are best addressed surgically, but small volume taps may be necessary to stabilize patients in preparation for operative repair.
6. **Small, loculated, or posteriorly located effusions** are technically more difficult to tap and have increased risk of complication. Echocardiographic guidance is paramount if pericardiocentesis is attempted.
7. **Purulent effusions.** While suspected purulent or tuberculous effusions are considered an indication for pericardiocentesis, grossly infected pericardial fluid should be managed surgically.
8. **Malignant effusion.** As stated previously, management of malignant effusions is controversial. Although pericardiocentesis is an effective and proven first-line therapy, recurrent effusions should be considered for pericardial window.

IV. PERICARDIOCENTESIS VERSUS SURGICAL MANAGEMENT (Table 69.1). The choice of procedure for pericardial drainage varies depending on the underlying etiology of the effusion, chronicity, size, hemodynamic impact, and suspected recurrence rate. Surgical techniques include complete pericardiectomy, partial pericardiectomy, subxiphoid pericardiectomy, anterior transthoracic window, and pleuropericardial window—collectively carrying an 80% to 90% success rate depending on the patient and indication. When comparing with pericardiocentesis for drainage of effusions, however, the first surgical option is typically pericardial window. Pericardiectomy is typically limited to permanent constriction.

There is a dearth of prospective data regarding the best approach to managing pericardial effusions. Most of the data are empirical and management is often clinician-, institution-, and patient-dependent. General recommendations for percutaneous versus surgical management of effusions are listed in Table 69.1.

V. PATIENT PREPARATION. Ideally, pericardiocentesis is performed in a laboratory equipped for fluoroscopy and invasive hemodynamic monitoring.

A. Informed consent. Patients should receive a clear explanation of the risks and benefits of pericardiocentesis, including the rationale for performing the procedure.

B. Monitoring. Patients should have heart rate, blood pressure, and oxygen saturations measured throughout the procedure. In addition, electrocardiographic monitoring is necessary. Worsening hemodynamics or falling oxygenation should alert the operator to the possibility of a procedural complication. Frequent ectopy (premature ventricular contractions, premature atrial contractions, or nonsustained ventricular tachycardia) may indicate impending perforation of a cardiac chamber. Some authorities recommend pulmonary artery catheter placement prior to performing a tap; however, for routine cases, this is not necessary.

C. Sedation. Pericardiocentesis is an anxiety-producing procedure for the patient. Appropriate pain relief and sedation should be administered prophylactically when this is clinically indicated and where it will not interfere with an already tenuous hemodynamic or respiratory state.

VI. TECHNIQUES

A. Echo guided. Currently, ultrasound-guided pericardiocentesis is the standard approach at most institutions. Patients are placed supine or in a slightly left lateral decubitus position. The head is elevated approximately 30°, and a complete echocardiographic evaluation is performed with standard parasternal, apical, and subcostal

TABLE 69.1 Approach to Pericardial Drainage

Pericardiocentesis	Surgical management
Most cases of cardiac tamponade	Cardiac tamponade due to aortic dissection or cardiac trauma; recurrent tamponade
Large or symptomatic effusions refractory to medical treatment	Recurrence of large chronic effusions after failed pericardiocentesis
High suspicion of tuberculous, purulent, or neoplastic pericarditis	Purulent effusion
	Loculated effusion
	Need for pericardial biopsy
	Coagulopathy

views. Attention is focused on the site where the greatest amount of pericardial fluid is closest to the skin surface. In addition, the liver should be identified to avoid accidental laceration during the procedure. Because it is air filled, lung tissue will block ultrasound waves and preclude imaging of the heart; consequently, the risk of pneumothorax is low if a good echocardiographic window is selected for the tap. While imaging, it is imperative to take note of the distance to the fluid pocket as well as **the probe trajectory**. Failure to maintain an appropriate trajectory is a common cause of failure in accessing a pericardial effusion percutaneously. Obviously, the trajectory of the needle during the pericardiocentesis should be identical to the trajectory of the echocardiographic probe when imaging. The echo may be used in real time to help monitor the needle tip during insertion, especially with the assistance of a second operator, although real time is not always necessary in the case of large effusions.

1. **Prepping the patient.** Once the best window is selected, the probe's location is marked with a permanent marker and scrubbed with sterile chlorhexidine-alcohol or povidone-iodine solution. The entire torso is draped with sterile towels. The patient should not move between the echocardiographic examination and the procedure.
2. **Marking the needle.** Using a sterile pen, a mark can be made on the pericardiocentesis needle at the approximate distance between the skin and effusion that was noted on the echocardiogram. The needle used should be 5 to 8 cm in length, with a short bevel to lessen the risk of lacerating structures at the needle's tip. In some instances, particularly in obese patients, longer needles will be needed. It is imperative to know in these situations how far the needle should be inserted before pericardial fluid is expected.
3. **Anesthetic.** Local anesthetic (e.g., 1% lidocaine) is applied to the skin over the mark. Then deeper anesthetic is given over the superior aspect of the rib (if a chest wall approach is used).
4. **Entering the pericardium.** Using a three-way stopcock, an 18G Cook needle is attached to a syringe that contains a few more milliliters of local anesthetic. The needle is advanced through the anesthetized tract, over the rib, along the same trajectory as the echocardiographic probe, until fluid is aspirated. Alternatively, a sheathed catheter may be used instead of the Cook needle. Upon aspiration of fluid, the catheter is advanced over the needle, and the needle is withdrawn.
5. **Confirming catheter/needle placement.** While imaging from a remote location, agitated saline may be injected through the stopcock. **The appearance of bubbles in the pericardial space confirms an appropriate location.** Bubbles appearing within a cardiac chamber suggest that the heart has been perforated and that the needle or catheter should be withdrawn. If agitated saline cannot be visualized, one should consider an intrathoracic needle position. If effusions are large, the agitated saline may not be visible from all echocardiographic windows; occasionally, it may be necessary to reinject saline and image from an alternative location.
6. **Placing the pericardial catheter.** Once the intrapericardial position is confirmed, a floppy-tipped, 0.035" guidewire is inserted through the needle into the pericardial space. A blade scalpel is then used to nick the skin over the needle, the needle is withdrawn, and a 6F dilator is used to broaden the tract into the pericardium. Finally, the dilator is removed and a 6F to 8F pigtail angiocatheter with side holes is threaded over the wire well into the pericardial space. The wire is removed, and catheter placement can again be confirmed with agitated saline injection. With a three-way stopcock, the catheter is then attached to a 30-cm length of plastic tubing, which in turn may be connected to a vacuum bottle or drainage bag. The catheter should be sutured in place.
7. **Bloody pericardial fluid or frank blood?** Occasionally, very bloody fluid may be aspirated during pericardiocentesis, and confirmation of the needle placement may be difficult. Therefore, differentiating between blood (chamber perforation)

and bloody effusion can be challenging. A few milliliters of the aspirate can be placed on a gauze pad; classical teaching suggests that if the fluid coagulates, it is blood from chamber perforation. Conversely, fluid that spreads out on the gauze forming a pinkish halo suggests an intrapericardial origin. In reality, effusions caused by cardiac rupture, dissection, or ongoing bleeding into the pericardial space may clot upon aspiration; this fluid should be sent for hematocrit (to confirm that it is blood), and cardiothoracic surgery consultation should take place emergently.

B. Electrocardiographic guidance. Electrocardiographically guided pericardiocentesis may be used if echocardiography is unavailable or it may be used in conjunction with echocardiography. However, most authorities agree that electrocardiographic guidance adds little to the safety of a carefully performed echocardiographically guided procedure. If used instead of echocardiography, a subxiphoid approach is typically preferred:

- (1) The patient is positioned at a 45° incline.
- (2) Electrocardiographic limb leads are attached to the patient in the usual fashion.
- (3) The xiphoid process is identified, and a point just inferior and to one side of the process is marked.
- (4) The region is prepared and draped sterilely, and local anesthetic is given around the mark with a 25G needle.
- (5) A 21G steel spinal needle is attached to a syringe filled with local anesthetic. The needle should be approximately 10 cm long. With a sterile alligator clip, the V lead of the electrocardiography monitor is attached to the metal hub of the spinal needle.
- (6) The needle should be directed posteriorly at approximately 90° to the patient until the tip is below the costal margin. Then the hub of the needle should be depressed toward the patient's skin and advanced toward the left shoulder at an angle of 15° to 30° to the patient. Local anesthetic is injected as needed, and gentle suction should be applied to the syringe when advancing.
- (7) ST elevations or premature ventricular contractions on the electrocardiography monitor indicate that the needle is encountering the right ventricle. PR-segment elevation or frequent premature atrial contractions (PAC) indicate that the needle is penetrating the right atrium. In the average adult, the distance from skin to pericardium is approximately 6 to 8 cm (1).
- (8) Once in the pericardial space, a catheter may be placed as described previously.

C. Fluoroscopic guidance. Fluoroscopy can be used as well to guide pericardiocentesis, although this approach has largely been supplanted by echocardiography. With fluoroscopy, a subxiphoid approach is again used. The needle is directed to the left shoulder and toward the anterior diaphragmatic border of the right ventricle. Upon penetration into the pericardial space, needle position may be confirmed with injection of radiopaque contrast media. A drainage catheter may then be placed as described earlier.

D. Blind approach. In emergent conditions, blind pericardiocentesis may be necessary. A subxiphoid approach is used as described above. However, because of the significantly higher rates of complications, blind taps should be avoided unless absolutely necessary.

VII. DIAGNOSTIC STUDIES. If the cause of the pericardial effusion is not clear, fluid should be sent for analysis. The primary causes of idiopathic effusions depend somewhat on the patient population but include tuberculosis (TB), viral infection, uremia, collagen vascular disease, neoplasia, surgery, and myocardial infarction. Therefore, all fluid from idiopathic effusions should be sent for bacterial, mycobacterial, and viral cultures; cytologic examination; acid-fast bacillus smear; cell count; protein; glucose; and lactate dehydrogenase. If TB is suspected, evaluate for adenosine deaminase, interferon gamma, pericardial lysozyme, and polymerase chain reaction. If malignancy is suspected, tumor

markers can be sent for evaluation. Blood samples should be sent for chemistry, complete blood count, blood cultures (if bacterial infection is likely), thyroid-stimulating hormone, erythrocyte sedimentation rate/C-reactive protein, antinuclear antibody, and rheumatoid factor (if connective tissue disease is suspected). Consideration should also be given to conducting a tuberculin purified protein derivative skin test.

VIII. COMPLICATIONS. Using echocardiographic guidance, the rate of complications is low. The largest series of echo-guided pericardiocentesis comes from the Mayo Clinic. Among the 1,127 procedures studied, major complications occurred in 1.2% of cases, and these included one death from right ventricular perforation, five nonfatal perforations that required surgery, one intercostal artery laceration, five pneumothoraces, one episode of sustained ventricular tachycardia, and one episode of bacteremia. Minor complications occurred 3.5% of the time and included 11 chamber perforations that sealed spontaneously, 8 self-limited pneumothoraces, 9 pleuropericardial fistulas, and 2 episodes of nonsustained ventricular tachycardia.

Fluoroscopy appears to be associated with higher rates of complications. In one series of 352 procedures, complications included 2 (0.6%) deaths, 23 (5.6%) chamber perforations (3 requiring surgery), 5 (1.4%) arterial bleeds (3 diaphragmatic, 1 posterior descending artery, and 1 left internal mammary artery), and 2 pneumothoraces (2).

Blind pericardiocentesis has been associated with morbidity rates as high as 20% and mortality rates as high as 6%.

Therefore, complications are relatively rare in experienced centers, although one must be mindful of the following:

- A. Pneumothorax.** This is usually effectively avoided with echocardiographic imaging. If the parasternal approach is used, remaining close to the sternum decreases the risk of pneumothorax.
- B. Chamber entry/cardiac laceration.** This is usually asymptomatic and self-sealing, particularly if the left ventricle is entered. Right ventricular perforations have a somewhat higher likelihood of bleeding when perforated, but right atrial lacerations carry the highest risk. If laceration is suspected, the needle or catheter should be withdrawn and the patient should be observed overnight in an intensive care setting. Serial echocardiograms are indicated to assess for changes in effusion size.
- C. Arterial laceration.** The left internal thoracic/mammary artery runs down the chest wall about 1 to 2 cm lateral to the sternum, with the vein running slightly more medial (3). Left chest wall and subxiphoid approaches must take this anatomy into consideration. The posterior descending artery can be lacerated on subxiphoid approaches if the needle is aimed too medially. On a chest wall approach, the intercostal arteries are avoided by passing the catheter just superior to the rib.
- D. Infection.** Sterile technique during the procedure and meticulous catheter care afterward if a drain is left in place minimize this risk. As the Mayo series suggests, the risk of catheter-related infection is very low, even among cancer patients.
- E. Death.** This is exceptionally rare when procedures are performed by experienced operators with echocardiographic guidance.

IX. POSTPROCEDURE CARE

- A. Chest radiography.** A postprocedure chest film should be obtained in all patients to exclude pneumothorax.
- B. Monitoring.** Patients should be observed for 1 to 2 hours following the pericardiocentesis. Patients without significant comorbidities who have uncomplicated diagnostic taps do not require inpatient care following the procedure.
- C. Drain care.** Care of an indwelling pericardial catheter is similar to that for any central line. After the catheter is sutured in place, the site is treated with an antibacterial ointment and then dressed sterily. The dressing should be changed every 2 or 3 days.

1. The drain should be aspirated every 6 hours. Continuous drainage can also be used, but the risk of catheter obstruction is higher. Following aspiration, the catheter is flushed with sterile or heparinized saline.
 2. If the fluid becomes purulent or the patient becomes septic, the catheter must be removed.
 3. Strict record of the volume of fluid draining from the catheter must be kept. The catheter is typically left in place for 1 to 2 days, but extended drainage has been associated with lower rates of effusion recurrence. When the drainage is < 25 to 50 mL/d, the catheter can be removed.
- D. Follow-up echocardiography.** Before pulling the drain, an echocardiogram should be obtained to ensure resolution of the effusion.
- E. Patient care.** Patients may be ambulatory with the drain securely in place. Pericardial pain is best managed with nonsteroidal anti-inflammatory medications.

ACKNOWLEDGMENTS: *The authors wish to thank Christian Gring MD for his contribution to an earlier edition of this chapter.*

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Commonly Used Cardiovascular Formulae

GENERAL HEMODYNAMICS

Mean arterial pressure (mm Hg) = Diastolic blood pressure (BP) + $\frac{1}{3}$ (Systolic BP – Diastolic BP)

Stroke volume (mL) = End-diastolic volume – End-systolic volume

Cardiac output (L/min) = Heart rate \times Stroke volume

Ohms law $V = IR$

V = Pressure difference across the system

I = Cardiac output or flow

R = Resistance across the system

Systemic vascular resistance (Wood unit) = $\frac{\text{Mean arterial pressure} - \text{Central venous pressure}}{\text{Cardiac output}}$

Pulmonary vascular resistance (Wood unit) = $\frac{\text{Mean PA pressure} - \text{Mean PCWP}}{\text{Cardiac output}}$

PA, pulmonary artery; PCWP, pulmonary capillary wedge pressure

1 Wood unit = 80 dynes/s/cm⁵

Pulmonary vascular resistance (echo) (Wood unit) = $\left(\frac{\text{Tricuspid regurgitation velocity}}{\text{RVOT VTI}} \right) \times 10 + 0.16$

RVOT, right ventricular outflow tract; VTI, Velocity Time Integral

Transpulmonary gradient (mm Hg) = Mean PAP – PCWP

PAP, pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure

Fick equation

Cardiac output (L/min) = $\frac{\text{Vo}_2 \text{ (mL/min)}}{1.36 \text{ (mL O}_2\text{/g Hgb)} \times \text{Hgb (g/dL)} \times 10 \text{ (dL/L)} [\text{SaO}_2 - \text{SvO}_2]}$

Vo₂ (oxygen consumption)

Cardiac index (L/min/m²) = $\frac{\text{Cardiac output (L/min)}}{\text{Body surface area (m}^2\text{)}}$

Body surface area (m²) = [Height (cm) + Weight (kg) – 60]/100

Dubois formula for body surface area (m²) = $\sqrt{\frac{\text{Height (cm)} \times \text{Weight (kg)}}{3,600}}$

Stroke work (g-m/beat) = Stroke volume \times Mean arterial pressure $\times 0.0144$

Stroke work index (g-m/m²/beat) = $\frac{\text{Stroke work}}{\text{Body surface area}}$

Coronary flow reserve = $\frac{\text{Peak coronary velocity at maximal hyperemia}}{\text{Peak coronary velocity at baseline}}$

Fractional flow reserve = $\frac{\text{Mean distal coronary pressure beyond stenosis}}{\text{Mean aortic pressure}}$

VALVULAR DISEASE AND LEFT VENTRICULAR (LV) FUNCTION

Gorlin equation

Aortic valve area (cm²) =
$$\frac{\text{Cardiac output (mL/min)}}{44.3 \times \text{Systolic ejection period (s/beat)} \times \text{Heart rate (beats/min)} \times \sqrt{\text{Mean gradient}}}$$

Mitral valve area (cm²) =
$$\frac{\text{Cardiac output (mL/min)}}{38 \times \text{Diastolic filling period (s/beat)} \times \text{Heart rate (beats/min)} \times \sqrt{\text{Mean gradient}}}$$

Hakki equation

Aortic valve area (cm²) = $\frac{\text{Cardiac output}}{\sqrt{\text{Peak to peak gradient}}}$ or $\frac{\text{Cardiac output}}{\sqrt{\text{Mean gradient}}}$

Mitral valve area (cm²) = $\frac{\text{Cardiac output}}{\sqrt{\text{Mean gradient}}}$

Simplified Bernoulli equation

Pressure difference = $4 v^2$

If proximal velocity > 1 m/s, then pressure difference = $4 [(\text{distal jet velocity})^2 - (\text{proximal velocity})^2]$

Continuity aortic valve area (cm²) = $\text{Diameter}_{\text{LVOT}}^2 \times 0.785 \times \frac{\text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{Aortic valve}}}$

LVOT, left ventricular outflow tract; VTI, velocity time integral

Dimensionless index = $\frac{\text{VTI}_{\text{LVOT}}}{\text{VTI}_{\text{Aortic valve}}}$

VTI, velocity time integral; LVOT, left ventricular outflow tract

Stroke volume (mL) = $\text{Diameter}_{\text{LVOT}}^2 \times 0.785 \times \text{VTI}_{\text{LVOT}}$

VTI, velocity time integral; LVOT, left ventricular outflow tract

Aortic regurgitant fraction (%) = $\frac{\text{Aortic regurgitant volume}}{\text{LVOT stroke volume}} \times 100$

LVOT, left ventricular outflow tract

Mitral valve area (mitral stenosis) (cm²) = $\frac{220}{\text{Pressure half time}}$

Tricuspid valve area (tricuspid stenosis) (cm²) = $\frac{190}{\text{Pressure half time}}$

Pressure half time (ms) = $0.29 \times \text{Deceleration time}$

Proximal isovelocity surface area (PISA) method in mitral regurgitation

$$\text{Regurgitant orifice area (cm}^2\text{)} = \frac{6.28 \, r^2 \times \text{Aliasing velocity}}{\text{Mitral regurgitation velocity}}$$

r , radius of PISA

Simplified PISA when aliasing velocity ~ 40 cm/s and peak continuous wave mitral regurgitation velocity ~ 5 m/s

$$\text{Regurgitant orifice area (cm}^2\text{)} = \frac{r^2}{2}$$

r , radius of PISA

Mitral regurgitant volume (mL) = $1.9r^2 \times \text{Aliasing velocity}$

r , radius of PISA

$$\text{Mitral regurgitant fraction (\%)} = \frac{\text{Mitral regurgitant volume}}{\text{Mitral valve flow}} \times 100$$

$$\text{Fractional shortening (\%)} = \frac{\text{LVED dimension} - \text{LVES dimension}}{\text{LVED dimension}} \times 100$$

LVED, left ventricular end diastole; LVES, left ventricular end systole

$$\text{Ejection fraction (\%)} = \frac{\text{End diastolic volume} - \text{End systolic volume}}{\text{End diastolic volume}} \times 100$$

$$\text{Estimated pulmonary artery systolic pressure (mm Hg)} = \text{RA pressure} + 4 \times (\text{Peak tricuspid regurgitation velocity})^2$$

RA, right atrium

$$\text{Estimated pulmonary artery end-diastolic pressure (mm Hg)} = \text{RA pressure} + 4 \times (\text{Pulmonary regurgitation end-diastolic velocity})^2$$

RA, right atrium

Assessment of right atrial (RA) pressure (by echo)

IVC diameter (cm)	IVC collapse	Estimated RA pressure (mm Hg)
≤ 2.1	$> 50\%$	3 (range 0–5)
≤ 2.1	$< 50\%$	8 (range 5–10)
> 2.1	$> 50\%$	8 (range 5–10)
> 2.1	$< 50\%$	15 (range 10–20)

IVC, inferior vena cava

$$\text{Left atrial (LA) pressure (mm Hg)} = \text{Systolic blood pressure} - 4 \times (\text{Mitral regurgitation velocity})^2$$

$$\text{LV mass (area length)} = 1.05\{[5/6 A1(a + d + t)] - [5/6 A2(a + d)]\}$$

A1 = area of LV short axis using epicardial perimeter

A2 = area of LV short axis using endocardial perimeter

t = myocardial thickness

a = long axis length from widest minor axis radius to apex

b = short axis radius

d = truncated long axis from widest short axis diameter to mitral annulus plane

$$Dp/dt = \frac{32,000 \text{ mm Hg}}{dt \text{ (in seconds)}}$$

Dt , time it takes velocity to go from 1 to 3 m/s

Tei index (myocardial performance index) =

$$\frac{\text{Isovolumic contraction time} + \text{Isovolumic relaxation time}}{\text{Ejection time}}$$

SHUNTS

$$\text{Shunt fraction } (Q_p/Q_s) = \frac{(SaO_2 - SvO_2)}{(PvO_2 - PaO_2)}$$

SaO_2 , systemic arterial oxygen saturation

SvO_2 , systemic venous oxygen saturation

PvO_2 , pulmonary venous oxygen saturation

PaO_2 , pulmonary arterial oxygen saturation

$$MvO_2 (\%) = \frac{3 \times (SVCsat) + (IVCsat)}{4}$$

MvO_2 , mixed venous saturation

SVC, superior vena cava

IVC, inferior vena cava

$$Q_p/Q_s \text{ (echo)} = \frac{RVOT \text{ Cross-sectional area} \times RVOT \text{ TVI}}{LVOT \text{ Cross-sectional area} \times LVOT \text{ VTI}}$$

RVOT, right ventricular outflow tract

VTI, velocity time integral

LVOT, left ventricular outflow tract

ELECTROPHYSIOLOGY/ECG

$$QT_c \text{ (ms)} = \frac{QT}{\sqrt{RR \text{ interval (seconds)}}}$$

$$\text{Heart rate (beats/min)} = \frac{60,000}{\text{Cycle length (ms)}}$$

Left ventricular hypertrophy

Limb lead criteria

- (1) R wave in lead I + S wave in lead III > 2.5 mV
- (2) R wave in aVL > 1.1 mV
- (3) R wave in aVF > 2.0 mV
- (4) S wave in aVR > 1.4 mV

Precordial lead criteria

- (1) R wave in V_5 or $V_6 > 2.6$ mV
- (2) R wave in V_6 + S wave in $V_1 > 3.5$ mV
- (3) Largest R wave + largest S wave in precordial leads > 4.5 mV

Cornell criteria

R wave in aVL + S wave in $V_3 > 2.0$ mV for females and 2.8 mV for males

Duke treadmill score (DTS)

DTS = Exercise time (minutes) – (5 × Maximal ST deviation) – (4 × Angina score)

0 = no angina

1 = nonlimiting angina

2 = angina limiting further testing

DTS ≤ -11 = high risk

DTS – 10 to 4 = moderate risk

DTS ≥ 5 = low risk

Age-predicted maximal heart rate (beats/min) = $220 - \text{Age}$

PHARMACODYNAMICS

Volume of distribution (L) = $\frac{\text{Amount of drug in body}}{\text{Plasma drug concentration}}$

Loading dose (mg) = $\frac{(\text{Volume of distribution}) \times (\text{Plasma drug concentration})}{(\text{Fraction of dose that is active}) \times (\text{Bioavailability of drug})}$

Clearance (L/h) = $\frac{\text{Rate of drug administration}}{\text{Steady-state plasma drug concentration}}$

Half-life (h) = $\frac{0.693 \times \text{Volume of distribution}}{\text{Clearance (L/h)}}$

MISCELLANEOUS

Cockcroft-Gault

Glomerular filtration rate (mL/min) = $\frac{[(140 - \text{Age}) \times \text{Weight (kg)}]}{72 \times \text{Creatinine}}$

If female, multiply by 0.85

Ankle-Brachial index = $\frac{\text{Pedal pressure}}{\text{Brachial pressure (higher of two sides)}}$

Law of Laplace

Wall tension = $\frac{\text{Pressure} \times \text{Radius}}{\text{Wall thickness}}$

Central perfusion pressure = Mean arterial pressure – Intracranial pressure

Assessment of appropriateness of ascending aorta size to height

$$\text{Aortic index} = \frac{\text{Maximal cross-sectional area of ascending aorta (cm}^2\text{)}}{\text{Height (m)}}$$

If ratio > 10, consider repair of aorta

Cholesterol mg/dL to mmol/L

1 mg/dL = 0.02586 mmol/L; 1 mmol/L = 38.7 mg/dL

Thus, 130 mg/dL = 3.45 mmol/L

Total cholesterol = LDL cholesterol + HDL cholesterol + 0.20 (Triglyceride level)

HDL, high-density lipoprotein; LDL, low-density lipoprotein

STATISTICS

	Disease present	Disease absent
Test result positive	a (True positive)	b (False positive)
Tests result negative	c (False negative)	d (True negative)

$$\text{Sensitivity} = \frac{a}{a + c}$$

$$\text{Specificity} = \frac{d}{b + d}$$

$$\text{Positive predictive value} = \frac{a}{a + b}$$

$$\text{Negative predictive value} = \frac{d}{c + d}$$

$$\text{Likelihood ratio for a positive test} = \frac{\text{Sensitivity}}{1 - \text{Specificity}} = \frac{a/a + c}{b/b + d}$$

$$\text{Likelihood ratio for a negative test} = \frac{1 - \text{Sensitivity}}{\text{Specificity}} = \frac{c/a + c}{d/b + d}$$

	Outcome positive	Outcome negative
Treated group	a	b
Control group	c	d

$$\text{Relative risk} = \frac{\text{Risk of outcome in treated group}}{\text{Risk of outcome in control group}} = \frac{a/a + b}{c/c + d}$$

$$\text{Relative risk reduction} = (1 - \text{Relative risk}) \times 100\%$$

Absolute risk reduction = Difference in risk of outcome between control group and treated group

$$\text{Absolute risk reduction} = c/c + d - a/a + b$$

$$\text{Number needed to treat} = \frac{1}{\text{Absolute risk reduction}}$$

$$\text{Odds ratio} = \frac{\text{Number of outcome events/Number of subjects}}{1 - (\text{Number of outcome events/Number of subjects})}$$

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